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(54) **MUTATED ANTITHROMBINS, A PROCESS FOR PREPARING THE SAME AND THEIR USE AS DRUGS**

MUTIERTE ANTITHROMBINE, VERFAHREN ZU DEREN HERSTELLUNG UND DEREN
VERWENDUNG ALS ARZNEIMITTEL

ANTITHROMBINES MUTÉES, LEUR PROCÉDÉ DE FABRICATION ET LEUR UTILISATION EN
TANT QUE MÉDICAMENTS

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Description

[0001] The present invention relates to mutated antithrombins and their use as drugs. The present invention also discloses a process for preparing mutated antithrombins.

Physiology

[0002] Systemic activation of the coagulation system is frequently observed in patients with severe sepsis and/or septic shock. Severe sepsis, as a complication of infection, is characterized by systemic inflammation, activation of proteolytic cascades, coagulation abnormalities (DIC), and various organ dysfunctions. Its more severe form, septic shock, associates in addition altered hemodynamic and impaired organ perfusion, aggravating further organ failure and frequently leading to death in multiorgan failure. Mortality in septic shock is high (40% to 50%), and rises tremendously with the number of failing organs, i.e. patients requiring renal replacement therapy for acute renal failure may have mortality rate above 80%. The initiating event for the development of severe sepsis is the activation of monocytes/macrophages by microbial antigens (i.e. lipopolysaccharide (LPS) liberated from Gram-negative bacteria, lipoteichoic acid from Gram-positive bacteria, fungal antigen) via binding to surface Toll-like receptors (Cohen J. The immunopathogenesis of sepsis. Nature. 2002; 420 :885-91).

Mechanistic

[0003] Monocyte/macrophages activation, potentially followed by endothelial cells activation, results in secretion of cytokine mediators (such as interleukin 6 (IL-6), tumor necrosis factor (TNF α) and chemokines, lipid mediators, adhesion molecules and tissue factor expression at the cell membrane, nitric oxide and oxygen reactive species formation). This step is followed by the activation of biological cascades including the coagulation and the complement, which contribute to the maintenance of the inflammatory reaction and coagulation activation. These events are fully adapted to eradicate microbial agents at the site of infection, but results in deleterious consequences, i.e. various organ failures, if they become widespread, unregulated and sustained. (Aird W. The role of the endothelium in severe sepsis and multiple organ dysfunction syndrome. Blood 2003 ; 101: 3765-77).

[0004] Tissue factor expression leads to uncontrolled generation of thrombin from its precursor molecule prothrombin. Endogenous anticoagulants, namely antithrombin (AT), protein C pathway and Tissue Factor Pathway Inhibitor, as well as the fibrinolytic system are activated and function to regulate thrombin generation and its consequences. However, blood levels of endogenous inhibitor are diminished due to their consumption onto their substrate, inhibited synthesis and cleavage by several proteases. Indeed, AT levels decrease precipitously in the early phases of severe sepsis. Fibrinolysis is rapidly inhibited by the production of plasminogen activator inhibitor-1. Thus, a procoagulant state develops in patients with sepsis potentially leading to overt disseminated intravascular coagulation (DIC), which has deleterious effects. Diffuse thrombus formation throughout microcirculation can compromise tissue perfusion to critical organs, and cellular effects of various coagulation proteins participate in the general inflammatory syndrome (Aird W. The role of the endothelium in severe sepsis and multiple organ dysfunction syndrome. Blood. 2003 ;101:3765-77). It is demonstrated that coagulation abnormalities in severe sepsis is associated with poor outcome. Notably, depletion of AT in septic shock portends a poor prognosis (Fourrier F. Septic shock, multiple organ failure, and disseminated intravascular coagulation: compared patterns of antithrombin III, protein C, and protein S deficiencies. Chest. 1992;101:816-823).

Antithrombin

[0005] Antithrombin plays an essential role in maintaining the fluidity of blood. Blood coagulation is mediated by a series of serine proteases. Antithrombin is a potent inhibitor of coagulation serine proteases, in particular, Factors IIa (thrombin), Xa, IXa and XIa. Interaction of AT with heparin-like glycosaminoglycans (HGAGs) on endothelial cells is important for the acceleration of thrombin inhibition by AT (Rosenberg RD. Biochemistry of heparin antithrombin interactions, and the physiologic role of this natural anticoagulant mechanism. Am J Med. 1989; 87:2S-9S). Indeed, thrombotic episodes have been observed in patients with congenital AT deficiency and in those with variant AT that lacks affinity for heparin suggesting that the interaction of AT with the endothelial cell surface heparin-like GAGs is important for regulation of the coagulation cascade by AT (Kuhle S, Lane DA, Jochmanns K, Male C, Quehenberger P, Lechner K, Pabinger I. Homozygous antithrombin deficiency type II (99 Leu to Phe mutation) and childhood thromboembolism. Thromb Haemost. 2001;86:1007-11). The physiological importance of antithrombin in preventing excessive coagulation is revealed by studies of individuals whose antithrombin levels are decreased due to heredity or acquired deficiency. Such persons are prone spontaneous thrombosis and the associated risks of disseminated intravascular coagulation, cardiac infarction, cerebrovascular accident and pulmonary embolism.

[0006] In addition, AT has been shown to exert cytoprotective properties, through its binding to the glycosaminoglycans

present on endothelial cells surface. Indeed, AT inhibits NFkB activation endothelial cells and monocytes, resulting in an increase in prostacyclin synthesis, a decrease in pro-inflammatory cytokines production (IL6 and TNF α), a reduction in tissue factor exposure on endothelial cells or monocytes, a reduction in platelet aggregation and in endothelial cells/neutrophil interactions. This effect is abolished by heparin, through a competition process. These cytoprotective effects were observed for AT concentrations ranging from 2.5 to 40 UI/ml (corresponding to 2.5 to 40 fold normal circulating AT levels).

Models of Sepsis

[0007] AT has been shown to be efficacious in several experimental models of sepsis and septic shock, regardless of the species investigated, as shown in baboons, dogs, sheep, rabbits, rats, and chicken embryos. AT in these models proved to be effective after inducing a sepsis or septic shock with different agents including live bacteria (*Escherichia coli*, *Klebsiella pneumoniae*) and bacterial lipopolysaccharide (LPS).

[0008] In a guinea pig model, it has been demonstrated that AT could prevent DIC and organ hemorrhage and improve mortality after infection with the Gram-positive bacterium *Staphylococcus aureus*.

[0009] Due to the missregulation of coagulation process during sepsis, some anticoagulants have been assayed in human, such as heparin or antithrombin.

[0010] Therapeutic doses of heparin (Corrigan JJ. Heparin therapy in bacterial septicemia. *J Pediatr.* 1977;91:695-700) or antithrombin (Schipper HG, Jenkins CSP, Kahl LH, ten Cate JW. Antithrombin III transfusion in disseminated intravascular coagulation. *Lancet.* 1978;1:854-856) have been used clinically for more than 20 years for the prevention and treatment of disseminated intravascular coagulation and sepsis, without any clear evidence of efficacy.

[0011] In order to treat activation of coagulation system and depletion of anticoagulant during severe sepsis, some studies have been made in patients by using high doses of antithrombin.

[0012] Warren et al. (High dose Antithrombin III in severe sepsis, 2008, *JAMA*, 286(15), 1869-1878) have tested the effect of administration of 30,000 IU (cumulative dose for a 4-day treatment) AT in patients in a randomized controlled trial study. Patients receiving AT treatment had plasma AT levels around 180% of normal circulating blood levels, these levels being lower than doses required to achieve a cytoprotective effect. This study could not demonstrate the efficiency of AT administration on patient survival. Moreover, the authors have demonstrated that the administration of AT, at this dosage, enhances the hemorrhagic risk in patients, said risk being increased when patient has received a concomitant administration of heparin.

[0013] A post-hoc analysis of this study focusing on DIC related to severe sepsis reported that this dosage of AT (30,000 IU over 4 days) increases the hemorrhagic risk in patients without heparinic treatment, compared to control treated with a placebo (Treatment effects of high-dose antithrombin without concomitant heparin in patients with severe sepsis with or without disseminated intravascular coagulation, 2006, *J. of Thrombosis and Haemostasis*, 4: 90-97),

[0014] Another study (Eisele et al. Antithrombin III in patients with severe sepsis, *intensive care Med.*, 1998, 24:663-672) has demonstrated that 18,000 UI (cumulative dose for a 5-day treatment) of AT have some benefits in patient survival, without bleeding problems. However, the panel of patients used in this study is too small to be sure that this dosage of AT has no effect on bleeding, and the dosage of AT remains under the identified efficient dosage of antithrombin necessary to provide a good cytoprotective effect: indeed, in this study, patients receiving AT treatment had AT levels ranging from 70 to 130% of normal circulating AT levels.

[0015] So there is a need to provide new medicines for treating severe sepsis, which enhances the anticoagulation system in the patient, but without causing hemorrhagic accidents.

[0016] Other anticoagulant has been tested in the treatment of severe sepsis.

[0017] Activated protein C (drotrecogin α) has been shown to reduce severe sepsis mortality in patients with the highest severity scores [Bernard GR, Vincent JL, Laterre PF, LaRosa SP, Dhainaut JF, Lopez-Rodriguez A, Steingrub JS, Garber GE, Helterbrand JD, Ely EW, Fisher CJ Jr; Recombinant human protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study group. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001;344:699-709]. In spite of the results of this study, the use of activated protein C remains controversial, as controversy regarding the efficacy/safety profile of this drug notably regarding bleeding. WO2005/007820 discloses the use of a mutated activated protein C variants, with reduced anticoagulant activity, for the treatment of pathologies requiring a cellular cytoprotection, but these variants have not been tested in clinical practice [Kerschen EJ, Fernandez JA, Cooley BC, Yang XV, Sood R, Mosnier LO, Castellino FJ, Mackman N, Griffin JH, Weiler H. Endotoxemia and sepsis mortality reduction by non-anticoagulant activated protein C. *J Exp Med.* 2007 Oct 1;204(10):2439-48].

[0018] Thus, it is important to provide a new medicine that can cure all the forms of severe sepsis, without causing any, or reduced only, hemorrhagic manifestation in patients.

[0019] So, one aim of the invention is to provide a new drug.

[0020] Also, another aim of the invention is to provide a new pharmaceutical composition comprising modified antithrombin as an active substance.

[0021] The description relates to the use of a composition comprising of at least a mutated antithrombin :

- having an anticoagulant activity substantially reduced with respect to the anticoagulant activity of the non mutated antithrombin, or
- having substantially no anticoagulant activity,

5 for the preparation of a drug intended for the prevention or the treatment of pathologies associated with cellular injury, such as infection, inflammation or hypoxic injury.

[0022] The invention relates to the use of a composition comprising at least a mutated antithrombin having an anticoagulant activity substantially reduced with respect to the anticoagulant activity of the non mutated antithrombin, or having substantially no anticoagulant activity, said mutated antithrombin having further:

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- a thrombin inhibitory activity substantially reduced, or substantially lost, or
- a factor Xa inhibitory activity reduced, or substantially lost, or
- a thrombin inhibitory activity and a factor Xa inhibitory activity substantially reduced, or substantially lost,

15 and said mutated antithrombin comprising at least one mutation chosen among the group constituted by:

- R393H, Pro394, Δ R393-S394, Δ R393, Δ S394, S394Q, S394E, N135Q-R393H, N135Q-S394Q, N135Q-S394E, N1350-Pro394, N135Q- Δ R393-S394, N135Q- Δ R393 and N135Q- Δ S394, the amino acid numbering referring to the antithrombin amino acid sequence represented by SEQ ID NO : 2,
- 20 - R425H, Pro426, Δ R425-S426, Δ R425, Δ S426, S426Q, S426E, N167Q-R425H, N167Q-S426Q, N167Q-S426E, N167Q-Pro426, N1670- Δ R425-S426, N167Q- Δ R425 and N167Q- Δ S426, the amino acid numbering referring to the antithrombin amino acid sequence represented by SEQ ID NO : 26,

25 for the manufacture of a medicament for the prevention or the treatment of infection, inflammation or hypoxic injury, in particular sepsis and ischemia/reperfusion related to stroke, ischemia/reperfusion related to surgery and ischemia/reperfusion related to organ transplantation.

[0023] The term «mutated antithrombin» designates an antithrombin, preferably a human antithrombin, comprising at least a substitution, insertion and/or deletion of one or more amino acids within its amino acid sequence.

[0024] The said mutated antithrombins can be prepared according to the method described in the experimental part I/.

30 **[0025]** The human antithrombin sequence is described in Olds R.J., Lane D.A., Chowdhury V., De Stefano V., Leone G. and Thein S.L. "Complete nucleotide sequence of the antithrombin gene: evidence for homologous recombination causing thrombophilia" Biochemistry. 32 (16), 4216-4224 (1993).

[0026] The human antithrombin sequence of the invention is a Homo sapiens serpin peptidase inhibitor, clade C (antithrombin), member 1 (SERPINC1), mRNA. Accession NM 000488, Version NM 000488.2, GI:50541941.

35 **[0027]** There are many references which describe said DNA sequence (with signal peptide) but they are not absolutely identical because of the many natural polymorphisms of antithrombin which generally do not change the properties, i.e. the anticoagulant properties, of the antithrombin.

[0028] The human aminosequence of antithrombin presents two forms: a "short form" (SEQ ID NO: 2) which does not comprise a signal peptide and a "long form" (SEQ ID NO: 26) which includes a signal peptide.

40 **[0029]** The signal peptide comprises 32 amino acids and is necessary for antithrombin secretion. It is removed during antithrombin processing and the plasma antithrombin circulates as the « short form »,

[0030] Accordingly, in the present invention, the mutated antithrombin amino acid sequences, represented by SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 62, 64, 66, 68 and 78 do not comprise the signal peptide and the mutated antithrombin amino acid sequences, represented, by SEQ ID NO: 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 70, 72, 45 74, 76 and 80 include the signal peptide.

[0031] The term « mutated antithrombin » as used herein, designates mutated antithrombins which are different from the naturally found mutated antithrombin (also called mutants of antithrombin) known in the art in that said mutated antithrombins of the invention have a reduced or no anticoagulant activity, and are able to compete *in vivo* with plasma antithrombin for glycosaminoglycan binding.

50 **[0032]** It has unexpectedly been found that the said mutated antithrombins according to the invention are able to prevent the undesired complications of anticoagulation, in particular hemorrhages, resulting from side effects of said anticoagulant activity of antithrombin.

[0033] The expression « mutated antithrombin having substantially no activity » designates a mutated antithrombin which has lost its capacity to inhibit coagulation.

55 **[0034]** The expression « mutated antithrombin having an anticoagulant activity substantially reduced with respect to the anticoagulant activity of the non-mutated antithrombin » designates a mutated antithrombin which has a reduced (2 to 20 fold reduced) capacity to inhibit coagulation compared to the wild type antithrombin.

[0035] The anticoagulant activity of mutated antithrombin will be evaluated in a purified system: mutated antithrombin

anti-Xa and anti-IIa inhibitory activities will be measured as described in Material and methods section.

[0036] The mutated antithrombin according to the invention has a cytoprotective activity. This "cytoprotective activity" confers to mutated antithrombin properties to protect cells against damage or cellular injuries, such as damage caused by inflammation, infection or ischemia/hypoxia.

[0037] The cytoprotective activity of mutated antithrombin are evaluated as described in Material and methods section: briefly, the pro-inflammatory cytokines levels are compared (IL6 and TNF α) in whole blood exposed to LPS, in the presence or in the absence of mutated antithrombin.

[0038] The expression "cellular injury" refers to a damage caused to the structure or function of the cell caused by an agent which may be physical or chemical. Cellular injury occurs when limits of adaptive response to a stimulus are exceeded.

[0039] Cellular injury can be caused by, but not limited to, inflammation, infection, hypoxia and ischemia/reperfusion.

[0040] Ischemia occurs when arterial flow is impeded by arteriosclerosis or by thrombi and is the most common cause of hypoxia, occurs during an inadequate oxygenation of the blood due to cardiorespiratory failure, or during a loss of oxygen-carrying capacity of the blood as in anemia or carbon monoxide poisoning.

[0041] Cellular injury can be reversible or irreversible. In the case of an irreversible injury, many cells will undergo apoptosis or necrosis. Necrosis, which is the more common type of cell death, is manifested by severe cell swelling or cell rupture, coagulation of cytoplasmic proteins, breakdown of cell organelles such as lysosomes, etc...

[0042] Since heparin may compete with the interaction between mutated antithrombin and cellular heparin-like glycosaminoglycans, the mutated antithrombin according to the invention is preferably not administered in patients that have received heparin treatment. Other anticoagulants can be used in association with the mutated antithrombin of the invention, provided that said association does not impair the cytoprotective activity of mutated antithrombin.

[0043] More preferably, the present invention relates to the use of a mutated antithrombin having an anticoagulant activity substantially reduced with respect to the anticoagulant activity of the non mutated antithrombin, or having substantially no anticoagulant activity, for the preparation of a drug intended for the prevention or the treatment of pathologies associated with cellular injury, such as infection, inflammation or hypoxic injury, said mutated antithrombin being administered in a patient in a need thereof at a concentration from about 0,5 to about 15 UI/ml, particularly from about 1 to about 7,5 UI/ml to reach about 100% to 750% of AT in plasma (cytoprotective effects were observed for AT concentrations more than to 250%, with plasmatic AT). 1 IU of antithrombin is defined as the amount of antithrombin contained in 1 mL of plasma, corresponding to a range from about 0.15g/L to about 0.3g/L of plasma.

[0044] According to the invention, mutated AT is thus preferably administered with a loading dose from about 3000 to about 22500 IU (40 a 300 IU/kg) followed by a continuous intravenous infusion from about 3000 to about 22500 IU (40 a 300 IU/kg) for a period of time from 2 to 7 days, preferably 4 days.

[0045] The invention relates to a method for the prevention or the treatment of pathologies associated with cellular injury, such as infection, inflammation hypoxia or ischemia/reperfusion injury, comprising the administering in a patient in a need thereof of a composition comprising at least one mutated antithrombin:

- having an anticoagulant activity substantially reduced with respect to the anticoagulant activity of the non mutated antithrombin, or
- having substantially no anticoagulant activity,

said composition being administered at a dosage from about 20 UI/kg/day to about 600 UI/kg/day, preferably from about 40 UI/kg/day to about 300 UI/kg/day.

[0046] In a preferred embodiment, the invention relates to the use of a composition comprising at least a mutated antithrombin defined above, for the preparation of a drug intended for the treatment or prevention of pathologies related to cellular ischemia/reperfusion injury, in particular selected from the group comprising: Inflammatory syndromes, cardiovascular diseases, neural or brain diseases, ischemia/reperfusion injury related to surgery, organ transplantation and ischemia/reperfusion injury related to stroke, or for the treatment or prevention of pathologies related to infections, in particular selected from the group comprising infectious diseases, and inflammation associated diseases.

[0047] An advantageous embodiment of the invention relates to the use of a composition comprising at least a mutated antithrombin above-defined, wherein said pathologies are selected from the group comprising: sepsis, severe sepsis or septic shock ischemic stroke, heat stroke, acute myocardial infarction, extremity ischemia, acute neurodegenerative disease, chronic neurodegenerative disease, such as Alzheimer's disease, Down syndrome, Huntington's disease, and Parkinson's disease, organ transplantation, chemotherapy, and radiation injury, such as brain radiation injury.

[0048] According to the invention, "hypoxic injury" means hypoxia or ischemia/reperfusion. Definition and classification of severe sepsis is known in the art, and for instance is disclosed in Levy, M.M., et al., (Levy, M.M., et al. Intensive Care Med, 2003. 29(4): p. 530-8.

[0049] A stroke (acute cerebrovascular attack) occurs when the blood flow to the brain is decreased or stopped.

[0050] In one preferred embodiment, the present invention relates to the use of mutated antithrombin as defined above

for the preparation of a drug/medicine intended for the prevention or the treatment of sepsis; i.e. systemic inflammatory response syndrome (SIRS) accompanying an infective disease. Examples of syndromes caused by the aggravation of sepsis include severe sepsis, septic shock, and multiple organ dysfunction syndrome.

[0051] In one particular embodiment, the invention relates to the above-mentioned use, wherein said mutated antithrombin has:

- a thrombin inhibitory activity substantially reduced, or substantially lost, or
- a factor Xa inhibitory activity reduced, or substantially lost, or
- a thrombin inhibitory activity and a factor Xa inhibitory activity substantially reduced, or substantially lost.

[0052] The complete anticoagulant activity of antithrombin is achieved by the inhibition of the pro-coagulating activity of thrombin and factor Xa. Therefore, in order to reduce the anticoagulant activity of antithrombin it is possible to reduce, by mutation, its ability to inhibit thrombin, and/or factor Xa. Preferably, in order to completely reduce the anticoagulant activity of antithrombin, both of the thrombin and factor X inhibitory activity of antithrombin should be inactivated.

[0053] The thrombin inhibitory or factor Xa activity is "substantially reduced" means that the activity of antithrombin to inhibit thrombin or factor Xa is reduced compared to said activity in wild type antithrombin. Preferably, according to the invention, the thrombin inhibitory or factor Xa activity is considered as reduced when said activity represents from about 50% to about 5% of the thrombin inhibitory or factor Xa activity of the wild type antithrombin. Anti-Xa and anti-IIa inhibitory activities will be measured in a purified system as described in Material and methods section.

[0054] The thrombin inhibitory or factor Xa activity is "substantially lost" means that the activity of antithrombin to inhibit thrombin or factor Xa is absent compared to said activity in wild type antithrombin.

[0055] Anti-Xa and anti-IIa inhibitory activities are measured in a purified system as described in "Material and methods" section.

[0056] In one other preferred embodiment, the invention relates to the above-mentioned use, wherein said mutated antithrombin comprises at least one mutation within the region from the amino acid at position 380 to the amino acid at position 400, particularly within the region from the amino acid at position 390 to the amino acid at position 397, particularly within the region from the amino acid at position 390 to the amino acid at position 394, in particular at positions 393 or 394, the amino acid numbering referring to the antithrombin amino acid sequence represented by SEQ ID NO: 2, said mutation being a substitution, insertion or deletion.

[0057] The region from the amino acid at position 380 to the amino acid at position 400 is generally named "reactive center loop" (RCL). The residues in the RCL are numbered according to their positions relative to the scissile P1-P1' bond (non-primed numbers towards the N-terminus and primed numbers towards the C-terminus of the serpin). In particular, the region stretching from P14 to P4' (residues from 380 to 397) is complementary to the active site of its target protease. In particular, residues from P4 to P1' (residues from 390 to 394) directly interact within protease catalytic groove. In particular, residue P1 (393) is crucial for protease inhibition.

[0058] The mutated antithrombins of the invention can comprise others mutations, outside of the region from the amino acid at position 380 to the amino acid at position 400, provided there is no change in the above-mentioned properties of the mutated antithrombins.

[0059] In one other particular embodiment, the invention relates to the use as mentioned above, wherein said mutated antithrombin further comprises at least one mutation at the glycosylation sites at the amino acid at position 96, 135, 155 or 192, in particular at position 135, the amino acid numbering referring to the antithrombin amino acid sequence represented by SEQ ID NO: 2.

[0060] Glycosylation sites are necessary for antithrombin secretion when antithrombin is expressed in eukaryotic cells. However, removing one site does not impair antithrombin secretion while increases heparin-like glycosaminoglycans binding. Indeed, glycosylation chains are involved in antithrombin-cellular heparin-like glycosaminoglycans binding.

[0061] The interaction with cellular heparin-like glycosaminoglycans enhances the cytoprotective effect of antithrombin, and mutatis mutandis, the cytoprotective activity of mutated antithrombin according to the invention.

[0062] An advantageous embodiment of the invention relates to the use of a composition comprising at least a mutated antithrombin having an anticoagulant activity substantially reduced with respect to the anticoagulant activity of the non mutated antithrombin, or having substantially no anticoagulant activity, said mutated antithrombin having further:

- a thrombin inhibitory activity substantially reduced, or substantially lost, or
- a factor Xa inhibitory activity reduced, or substantially lost, or
- a thrombin inhibitory activity and a factor Xa inhibitory activity substantially reduced, or substantially lost,

and said mutated antithrombin comprising at least one mutation :

- within the region from the amino acid at position 380 to the amino acid at position 400, in particular at positions 393 or 394, the amino acid numbering referring to the antithrombin amino acid sequence represented by SEQ ID NO: 2, or
- within the region from the amino acid at position 412 to the amino acid at position 432, in particular at position 425 or 426, the amino acid numbering referring to the antithrombin amino acid sequence comprising the signal peptide,

said mutation being a substitution, insertion or deletion,

for the preparation of a drug intended for the prevention or the treatment of pathologies associated with infection, inflammation or hypoxic injury, in particular sepsis and ischemia/reperfusion related to stroke, ischemia/reperfusion related to surgery and ischemia/reperfusion related to organ transplantation.

[0063] A preferred embodiment of the invention relates to the use above mentioned, wherein said mutated antithrombin is an amino acid sequence selected from the group consisting of:

- SEQ ID NO:4, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:2, the substitution of the amino acid at position 393, by an Histidine (His),
- SEQ ID NO:6, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:2, the insertion of a Proline (Pro) between the amino acid at position 393 and the amino acid at position 394,
- SEQ ID NO:8, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:2, the deletion of the amino acid at position 393,
- SEQ ID NO:10, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:2, the deletion of the amino acid at position 394,
- SEQ ID NO:62, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:2, the substitution of the amino acid at position 394 by a Glutamine (Gln), and
- SEQ ID NO:64, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:2, the substitution of the amino acid at position 394 by a Glutamic acid (Glu).

[0064] Another preferred embodiment of the invention relates to the above defined use, wherein said mutated antithrombin is an amino acid sequence selected from the group consisting of:

- SEQ ID NO:14, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:2, the substitution of the amino acid at position 393, by an Histidine (His), and the substitution of the amino acid at position 135, by a Glutamine (Gln),
- SEQ ID NO:16, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:2, the insertion of a Proline (Pro) between the amino acid at position 393 and the amino acid at position 394, and the substitution of the amino acid at position 135, by a Glutamine (Gln),
- SEQ ID NO:18, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:2, the deletion of the amino acid at position 393 and at position 394,
- SEQ ID NO:20, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:2, the deletion of the amino acid at position 393 and the substitution of the amino acid at position 135, by a Glutamine (Gln),
- SEQ ID NO:22, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:2, the deletion of the amino acid at position 394 and the substitution of the amino acid at position 135, by a Glutamine (Gln),
- SEQ ID NO:24, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:2, the deletion of the amino acid at position 393 and at position 394, and the substitution of the amino acid at position 135, by a Glutamine (Gln),
- SEQ ID NO:66, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:2, the substitution of the amino acid at position 394 by a Glutamine (Gln), and the substitution of the amino acid at position 135, by a Glutamine (Gln), and
- SEQ ID NO:68, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:2, the substitution of the amino acid at position 394 by a Glutamic acid (Glu) and the substitution of the amino acid at position 135, by a Glutamine (Gln).

[0065] Another preferred embodiment of the invention related to the above mentioned use, wherein said mutated antithrombin comprises at least one mutation within the region from the amino acid at position 412 to the amino acid at position 432, particularly within the region from the amino acid at position 412 to the amino acid at position 429, particularly within the region from the amino acid at position 422 to the amino acid at position 426, in particular at position 425 or 426, the amino acid numbering referring to the antithrombin amino acid sequence comprising the signal peptide, repre-

sented by SEQ ID NO: 26, said mutation being a substitution, insertion or deletion.

[0066] The mutated antithrombins of the invention can comprise others mutations, outside of the region from the amino acid at position 412 to the amino acid at position 432, provided there is no change in the above-mentioned properties of the mutated antithrombins.

[0067] In a preferred embodiment, the invention relates to the use as mentioned herein, wherein said mutated antithrombin further comprises at least one mutation at the glycosylation sites at the amino acid at position 128, 167, 187 or 224, in particular at position 167 the amino acid numbering referring to the antithrombin amino acid sequence represented by SEQ ID NO: 26.

[0068] A more preferred embodiment of the invention relates to the above mentioned use, wherein said mutated antithrombin is an amino acid sequence selected from the group consisting of:

- SEQ ID NO:28, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:26, the substitution of the amino acid at position 425, by an Histidine (His), or
- SEQ ID NO:30, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:26, the insertion of a Proline (Pro) between the amino acid at position 425 and the amino acid at position 426, or
- SEQ ID NO:32, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:26, the deletion of the amino acid at position 425, or
- SEQ ID NO:34, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:26, the deletion of the amino acid at position 426,
- SEQ ID NO:70, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:26, and the substitution of the amino acid at position 426 by a Glutamine (Gln), and
- SEQ ID NO:72, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO: 26, and the substitution of the amino acid at position 426 by a Glutamic acid (Glu).

[0069] Another preferred embodiment of the invention relates to the use mentioned above, wherein said mutated antithrombin is an amino acid sequence selected from the group consisting of:

- SEQ ID NO:38, said amino acid sequence comprising in the sequence of antithrombin represented by SEQ ID NO:26, the substitution of the amino acid at position 425, by an Histidine (His), and the substitution of the amino acid at position 167, by a Glutamine (Gln),
- SEQ ID NO:40, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:26, the insertion of a Proline (Pro) between the amino acid at position 425 and the amino acid at position 426, and the substitution of the amino acid at position 167, by a Glutamine (Gln),
- SEQ ID NO:42, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:26, the deletion of the amino acid at position 425 and at position 426,
- SEQ ID NO:44, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:26, the deletion of the amino acid at position 425 and the substitution of the amino acid at position 167, by a Glutamine (Gln),
- SEQ ID NO:46, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:26, the deletion of the amino acid at position 426 and the substitution of the amino acid at position 167, by a Glutamine (Gln),
- SEQ ID NO:48, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:26, the deletion of the amino acid at position 425 and at position 426 and the substitution of the amino acid at position 167, by a Glutamine (Gln),
- SEQ ID NO:74, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:26, the substitution of the amino acid at position 426 by a Glutamine (Gln), and the substitution of the amino acid at position 167, by a Glutamine (Gln), and
- SEQ ID NO:76, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:26, the substitution of the amino acid at position 426 by a Glutamic acid (Glu) and the substitution of the amino acid at position 167, by a Glutamine (Gln).

[0070] The description describes the use of a combination comprising

- a first antithrombin consisting of at least one mutated antithrombin having a substantially reduced anticoagulant activity, or substantially no anticoagulant activity according herein, and
- a second antithrombin consisting of at least an antithrombin, having an anticoagulant activity similar to that of the wild type antithrombin

as a combination product for the preparation of a drug intended for the prevention or the treatment of pathologies associated with cellular injury, such as infection, inflammation or hypoxic injury, said combination product being possibly used for a simultaneous, sequential or separate administration, said first and said second antithrombins being in a predetermined weight ratio, preferably in a respective weight ratio of about 9:1 to about 1:4, preferably from about 4:1 to about 1:2, more preferably from about 2:1 to about 1:2.

[0071] The invention also relates to the use of a combination comprising:

- a first antithrombin consisting of at least one mutated antithrombin having a substantially reduced anticoagulant activity, or no anticoagulant activity according to any one of claims 1 to 3, and
- a second antithrombin consisting of at least an antithrombin, having an anticoagulant activity similar to that of the wild type antithrombin

as a combination product for the manufacture of a medicament for the prevention or the treatment of infection, inflammation or hypoxic injury, said combination product suitable for a simultaneous, sequential or separate administration, said first and said second antithrombins being in a predetermined weight ratio, preferably in a respective weight ratio of about 9:1 to about 1:4.

[0072] The invention also relates to the use of a combination comprising:

- a first antithrombin consisting of at least one mutated antithrombin having a substantially reduced anticoagulant activity, or no anticoagulant activity according to any one of claims 1 to 3, and
- a second antithrombin consisting of at least an antithrombin, having an anticoagulant activity similar to that of the wild type antithrombin

as a combination product for the manufacture of a medicament for the prevention or the treatment of sepsis, said combination product suitable for a simultaneous, sequential or separate administration, said first and said second antithrombins being in a predetermined weight ratio, preferably in a respective weight ratio of about 9:1 to about 1:4.

[0073] According to the invention, the terms "a first antithrombin consisting of at least one mutated antithrombin" refer to the mutated antithrombin as mentioned above.

[0074] According to the invention, the terms "a second antithrombin consisting of at least an antithrombin, having an anticoagulant activity similar to that of the wild type antithrombin" refer to any antithrombin having no mutation and corresponding to wild type antithrombin, or antithrombin having at least one mutation, said mutation not affecting the anticoagulant activity of said second antithrombin.

[0075] Thus, the second antithrombin of the invention may have a mutation in one or more glycosylation site, in particular a mutation in the residue at the position 135 of the sequence SEQ ID NO 2 or in the residue at position 167 of the SEQ ID NO 26. These "mutated antithrombin" (a second antithrombin) retain their anticoagulant activity.

[0076] Since heparin may compete with the interaction between mutated antithrombin and cellular heparin-like glycosaminoglycans, the mutated antithrombin according to the invention is preferably not administered in patients that have received heparin treatment. Other anticoagulant can be used in association with the mutated antithrombin of the invention provided that said association does not impair the cytoprotective activity of mutated antithrombin.

[0077] The combination of the first antithrombin and the second antithrombin according to the invention is administered at a dosage from about 20 UI/kg/day to about 600 UI/kg/day, preferably from about 40 UI/kg/day to about 300 UI/kg/day.

[0078] In a case of a ratio first/second antithrombin corresponding to a ratio 9/1, said first antithrombin is administered at a dosage of from about 36 IU/kg/day to about 270 IU/kg/day and said second antithrombin is administered at a dosage of from about 4 IU/kg/day to about 30 IU/kg/day.

[0079] Also, the combination of said first and second antithrombin according to the invention can be administered in a patient in a need thereof at a concentration from about 0.5 to about 15 UI/ml, particularly from about 1 to about 7.5 UI/ml to reach about 100% to 750% of AT in plasma. The invention also relates to a method for the prevention or the treatment of pathologies associated with cellular injury, such as infection, inflammation or hypoxic injury, comprising the administering in a patient in a need thereof of a combination comprising:

- a first antithrombin consisting of at least one mutated antithrombin having a substantially reduced anticoagulant activity, or substantially no anticoagulant activity according herein, and
- a second antithrombin consisting of at least an antithrombin, having an anticoagulant activity similar to that of the wild type antithrombin

said combination being administered at a dosage from about 20 UI/kg/day to about 600 UI/kg/day, preferably from about 40 UI/kg/day to about 300 UI/kg/day.

[0080] The combination according to the invention confers a cytoprotective activity against cellular injury via both first antithrombin while presence of the second antithrombin reduces the hemorrhagic accident.

[0081] In a preferred embodiment, the invention relates to the use of a combination as mentioned above, as a combination product for the for the preparation of a drug intended for the treatment or prevention of pathologies related to cellular ischemia/reperfusion injury, in particular selected from the group comprising: Inflammatory syndromes, Cardiovascular diseases, Neural or Brain diseases, Ischemia/reperfusion injury related to surgery, and Ischemia/reperfusion injury related to organ transplantation, or for the treatment or prevention of pathologies related to infections, in particular selected from the group comprising: Infectious diseases, and Inflammation associated diseases.

[0082] A preferred embodiment of the invention relates to the use of a combination above defined, wherein said pathologies are selected from the group comprising sepsis, ischemic stroke, acute myocardial infarction, extremity ischemia acute neurodegenerative disease, chronic neurodegenerative disease, such as Alzheimer's disease, Down syndrome, Huntington's disease, and Parkinson's disease, organ transplantation, chemotherapy, and radiation injury, such as brain radiation injury.

[0083] In one preferred embodiment, the present invention relates to the use a composition as defined above for the preparation of a drug/medicine intended for the prevention or the treatment of sepsis; i.e. systemic inflammatory response syndrome (SIRS) accompanying an infective disease. Examples of syndromes caused by the aggravation of sepsis include severe sepsis, septic shock, and multiple organ dysfunction syndromes.

[0084] In one particular embodiment, the invention relates to the use of a combination mentioned above, wherein said mutated antithrombin has:

- a thrombin inhibitory activity substantially reduced, or substantially lost, or
- a factor Xa inhibitory activity reduced, or substantially lost, or
- a thrombin inhibitory activity and a factor Xa inhibitory activity substantially reduced, or substantially lost.

[0085] A more particular embodiment of the invention relates to the use of a combination above-mentioned, wherein said first antithrombin comprises at least one mutation within the region from the amino acid at position 380 to the amino acid at position 400, particularly within the region from the amino acid at position 390 to the amino acid at position 397, particularly within the region from the amino acid at position 390 to the amino acid at position 394, in particular at positions 393 or 394, the amino acid numbering referring to the antithrombin amino acid sequence represented by SEQ ID NO: 2, said mutation being a substitution, insertion or deletion, and wherein said second antithrombin is the wild type antithrombin.

[0086] In an advantageous embodiment, the present invention relates to the use such as defined above, wherein said first antithrombin is an amino acid sequence selected from the group consisting of:

- SEQ ID NO:4, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:2, the substitution of the amino acid at position 393, by an Histidine (His),
- SEQ ID NO:6, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:2, the insertion of a Proline (Pro) between the amino acid at position 393 and the amino acid at position 394,
- SEQ ID NO:8, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:2, the deletion of the amino acid at position 393,
- SEQ ID NO:10, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:2, the deletion of the amino acid at position 394,
- SEQ ID NO:18, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:2, the deletion of the amino acid at position 393 and at position 394,
- SEQ ID NO:62, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:2, and the substitution of the amino acid at position 394 by a Glutamine (Gln), and
- SEQ ID NO:64, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:2, and the substitution of the amino acid at position 394 by a Glutamic acid (Glu),

and said second antithrombin consists of SEQ ID NO:2.

[0087] The above mentioned combination contains at least one mutated first antithrombin having one or two mutations in the "reactive center loop" of antithrombin, in association with the wild type antithrombin.

[0088] In an advantageous embodiment, the present invention relates to the use of a composition In such as defined above, wherein said first antithrombin further comprises at least one mutation at the glycosylation sites at the amino acid at position 96, 135, 155 or 192, in particular at position 135, the amino acid numbering referring to the antithrombin amino acid sequence represented by SEQ ID NO: 2.

[0089] Another advantageous embodiment of the present invention relates to the use such as defined above, wherein said first antithrombin is an amino acid sequence selected from the group consisting of:

- SEQ ID NO:14, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:2, the substitution of the amino acid at position 393, by an Histidine (His), and the substitution of the amino acid at position 135, by a Glutamine (Gln),
- SEQ ID NO:16, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:2, the insertion of a Proline (Pro) between the amino acid at position 393 and the amino acid at position 394, and the substitution of the amino acid at position 135, by a Glutamine (Gln),
- SEQ ID NO:20, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:2, the deletion of the amino acid at position 393 and the substitution of the amino acid at position 135, by a Glutamine (Gln),
- SEQ ID NO:22, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:2, the deletion of the amino acid at position 394 and the substitution of the amino acid at position 135, by a Glutamine (Gln),
- SEQ ID NO:24, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:2, the deletion of the amino acid at position 393 and at position 394, and the substitution of the amino acid at position 135, by a Glutamine (Gln),
- SEQ ID NO:66, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:2, the substitution of the amino acid at position 394 by a Glutamine (Gln), and the substitution of the amino acid at position 135, by a Glutamine (Gln), and
- SEQ ID NO:68, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:2, the substitution of the amino acid at position 394 by a Glutamic acid (Glu) and the substitution of the amino acid at position 135, by a Glutamine (Gln),

and said second antithrombin consists of SEQ ID NO:2.

[0090] The above mentioned combination contains at least one mutated first antithrombin having one or two mutations in the "reactive center loop" of antithrombin, and a mutation at a glycosylation site, in association with the wild type antithrombin.

[0091] In another preferred embodiment, the invention relates to the use of a composition as defined above, wherein said second antithrombin comprises at least one mutation at the glycosylation sites at the amino acid at position 96, 135, 155 or 192, in particular at position 135, the amino acid numbering referring to the antithrombin amino acid sequence represented by SEQ ID NO: 2.

[0092] In another preferred embodiment, the invention relates to the use such as defined above, wherein said first antithrombin is an amino acid sequence selected from the group consisting of:

- SEQ ID NO:14, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:2, the substitution of the amino acid at position 393, by an Histidine (His), and the substitution of the amino acid at position 135, by a Glutamine (Gln),
- SEQ ID NO:16, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:2, the insertion of a Proline (Pro) between the amino acid at position 393 and the amino acid at position 394, and the substitution of the amino acid at position 135, by a Glutamine (Gln),
- SEQ ID NO:20, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:2, the deletion of the amino acid at position 393 and the substitution of the amino acid at position 135, by a Glutamine (Gln),
- SEQ ID NO:22, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:2, the deletion of the amino acid at position 394 and the substitution of the amino acid at position 135, by a Glutamine (Gln),
- SEQ ID NO:24, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:2, the deletion of the amino acid at position 393 and at position 394, and the substitution of the amino acid at position 135, by a Glutamine (Gln),
- SEQ ID NO:66, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:2, the substitution of the amino acid at position 394 by a Glutamine (Gln), and the substitution of the amino acid at position 135, by a Glutamine (Gln), and
- SEQ ID NO:68, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:2, the substitution of the amino acid at position 394 by a Glutamic acid (Glu) and the substitution of the amino acid at position 135, by a Glutamine (Gln),

and said second antithrombin consists of the amino acid sequence SEQ ID NO:78, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:2, the substitution of the amino acid at position 135, by a Glutamine (Gln).

[0093] The above mentioned combination contains at least one mutated first antithrombin having one or two mutations in the "reactive center loop" of antithrombin, and a mutation at a glycosylation site, in association with a second antithrombin having a mutation in a glycosylation site, but retaining its anticoagulant activity.

[0094] In one other particular embodiment, the invention discloses the use such as defined above, wherein said first antithrombin comprises at least one mutation within the region from the amino acid at position 412 to the amino acid at position 432, particularly within the region from the amino acid at position 412 to the amino acid at position 429, particularly within the region from the amino acid at position 422 to the amino acid at position 426, in particular at position 425 or 426, the amino acid numbering referring to the antithrombin amino acid sequence comprising the signal peptide, represented by SEQ ID NO: 26, said mutation being a substitution, insertion or deletion, and wherein said second antithrombin is the wild type antithrombin.

[0095] Another preferred embodiment of the invention relates to the use such as defined above, wherein said first antithrombin is an amino acid sequence selected from the group consisting of:

- SEQ ID NO:28, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:26, the substitution of the amino acid at position 425, by an Histidine (His), or
- SEQ ID NO:30, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:26, the insertion of a Proline (Pro) between the amino acid at position 425 and the amino acid at position 426, or
- SEQ ID NO:32, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:26, the deletion of the amino acid at position 425, or
- SEQ ID NO:34, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:26, the deletion of the amino acid at position 426,
- SEQ ID NO:42, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:26, the deletion of the amino acid at position 425 and at position 426,
- SEQ ID NO:70, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:26, and the substitution of the amino acid at position 426 by a Glutamine (Gln), and
- SEQ ID NO:72, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:26, and the substitution of the amino acid at position 426 by a Glutamic acid (Glu),

and second antithrombin consists of SEQ ID NO:26.

[0096] The above mentioned combination contains at least one mutated first antithrombin having one or two mutations in the "reactive center loop" of antithrombin, in association with the wild type antithrombin.

[0097] Also, in another preferred embodiment, the invention relates to the use such as defined above, wherein said first antithrombin further comprises at least one mutation at the glycosylation sites at the amino acid at position 128, 167, 187 or 224, in particular at position 167, the amino acid numbering referring to the antithrombin amino acid sequence represented by SEQ ID NO: 26.

[0098] Another preferred embodiment of the invention relates to the use as previously defined, wherein said first antithrombin is an amino acid sequence selected from the group consisting of:

- SEQ ID NO:38, said amino acid sequence comprising in the sequence of antithrombin represented by SEQ ID NO:26, the substitution of the amino acid at position 425, by an Histidine (His), and the substitution of the amino acid at position 167, by a Glutamine (Gln),
- SEQ ID NO:40, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:26, the insertion of a Proline (Pro) between the amino acid at position 425 and the amino acid at position 426, and the substitution of the amino acid at position 167, by a Glutamine (Gln),
- SEQ ID NO:44, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:26, the deletion of the amino acid at position 425 and the substitution of the amino acid at position 167, by a Glutamine (Gln),
- SEQ ID NO:46, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:26, the deletion of the amino acid at position 426 and the substitution of the amino acid at position 167, by a Glutamine (Gln),
- SEQ ID NO:48, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:26, the deletion of the amino acid at position 425 and at position 426 and the substitution of the amino acid at position 167, by a Glutamine (Gln),
- SEQ ID NO:74, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:26, the substitution of the amino acid at position 426 by a Glutamine (Gln), and the substitution of the amino acid at position 167, by a Glutamine (Gln), and
- SEQ ID NO:76, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:26, the substitution of the amino acid at position 426 by a Glutamic acid (Glu) and the substitution of the amino

acid at position 167, by a Glutamine (Gln),

and second antithrombin consists of SEQ ID NO:26.

[0099] The above mentioned combination contains at least one mutated first antithrombin having one or two mutations in the "reactive center loop" of antithrombin, and a mutation at a glycosylation site, in association with the wild type antithrombin.

[0100] Another preferred embodiment of the invention relates to the use such as defined above, wherein said second antithrombin comprises at least one mutation at the glycosylation sites at the amino acid at position 128, 167, 187 or 224, in particular at position 167, the amino acid numbering referring to the antithrombin amino acid sequence represented by SEQ ID NO: 26.

[0101] Another preferred embodiment of the invention relates to the use such as defined above, wherein said first antithrombin is an amino acid sequence selected from the group consisting of:

- SEQ ID NO:38, said amino acid sequence comprising in the sequence of antithrombin represented by SEQ ID NO:26, the substitution of the amino acid at position 425, by an Histidine (His), and the substitution of the amino acid at position 167, by a Glutamine (Gln),
- SEQ ID NO:40, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:26, the insertion of a Proline (Pro) between the amino acid at position 425 and the amino acid at position 426, and the substitution of the amino acid at position 167, by a Glutamine (Gln),
- SEQ ID NO:44, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:26, the deletion of the amino acid at position 425 and the substitution of the amino acid at position 167, by a Glutamine (Gln),
- SEQ ID NO:46, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:26, the deletion of the amino acid at position 426 and the substitution of the amino acid at position 167, by a Glutamine (Gln),
- SEQ ID NO:48, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:26, the deletion of the amino acid at position 425 and at position 426 and the substitution of the amino acid at position 167, by a Glutamine (Gln),
- SEQ ID NO:74, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:26, the substitution of the amino acid at position 426 by a Glutamine (Gln), and the substitution of the amino acid at position 167, by a Glutamine (Gln), and
- SEQ ID NO:76, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:26, the substitution of the amino acid at position 426 by a Glutamic acid (Glu) and the substitution of the amino acid at position 167, by a Glutamine (Gln),

and second antithrombin consists of the amino acid sequence SEQ ID NO:80, said amino acid sequence comprising, in the sequence of antithrombin represented by SEQ ID NO:26, the substitution of the amino acid at position 167, by a Glutamine (Gln).

[0102] The above mentioned combination contains at least one mutated first antithrombin having one or two mutations in the "reactive center loop" of antithrombin, and a mutation at a glycosylation site, in association with a second antithrombin having a mutation in a glycosylation site, but retaining its anticoagulant activity.

[0103] The description also describes a composition comprising at least

- a first antithrombin consisting of at least one mutated antithrombin having a substantially reduced anticoagulant activity, or substantially no anticoagulant activity according to any of claims 1 to 5 or 9, and
- a second antithrombin consisting of at least an antithrombin, having an anticoagulant activity similar to that of the wild type antithrombin

as a combination product for the preparation of a drug intended for the prevention or the treatment of pathologies associated with cellular injury, such as infection, inflammation or hypoxic injury., said combination product being possibly used for a simultaneous, sequential or separate administration, said first and said second antithrombins being in a predetermined weight ratio being in a predetermined weight ratio, preferably in a respective weight ratio of about 10:1 to about 1:5, preferably from about 5:1 to about 1:2, more preferably from about 2:1 to about 1:2.

[0104] The invention relates to a combination comprising at least

- a first antithrombin consisting of at least one mutated antithrombin having a substantially reduced anticoagulant activity, or no anticoagulant activity according to any of claims 1 to 3, and

- a second antithrombin consisting of at least an antithrombin, having an anticoagulant activity similar to that of the wild type antithrombin,

as a combination product for use in a method for the prevention or the treatment of infection, inflammation or hypoxic injury, said combination product being suitable for a simultaneous, sequential or separate administration, said first and said second antithrombins being in a predetermined weight ratio being in a predetermined weight ratio, preferably in a respective weight ratio of about 9:1 to about 1:4.

[0105] The invention also relates to a combination comprising at least

- a first antithrombin consisting of at least one mutated antithrombin having a substantially reduced anticoagulant activity, or no anticoagulant activity according to any of claims 1 to 3, and
- a second antithrombin consisting of at least an antithrombin, having an anticoagulant activity similar to that of the wild type antithrombin,

as a combination product for use in a method for the prevention or the treatment of sepsis, said combination product being suitable for a simultaneous, sequential or separate administration, said first and said second antithrombins being in a predetermined weight ratio being in a predetermined weight ratio, preferably in a respective weight ratio of about 9:1 to about 1:4.

[0106] In one preferred embodiment, the invention discloses a combination such as defined above, as a combination product for the preparation of a drug intended for the treatment or prevention of pathologies related to cellular ischemia/reperfusion injury, in particular selected from the group comprising: Inflammatory syndromes, Cardiovascular diseases, Neural or Brain diseases. Ischemia/reperfusion injury related to surgery, and Ischemia/reperfusion injury related to organ transplantation, or for the treatment or prevention of pathologies related to infections, in particular selected from the group comprising: infectious diseases, and inflammation associated diseases.

[0107] In another preferred embodiment, the invention relates to a combination above defined, wherein said pathologies are selected from the group comprising: sepsis, ischemic stroke, acute myocardial infarction, extremity ischemia, acute neurodegenerative disease, chronic neurodegenerative disease, such as Alzheimer's disease, Down syndrome, Huntington's disease, and Parkinson's disease, organ transplantation, chemotherapy, and radiation injury, such as brain radiation injury.

[0108] In other specific embodiment, the invention relates to a combination as defined above, wherein said first antithrombin has :

- a thrombin inhibitory activity substantially reduced, or substantially lost, or
- a factor Xa inhibitory activity reduced, or substantially lost, or
- a thrombin inhibitory activity and a factor Xa inhibitory activity substantially reduced, or substantially lost.

[0109] Another preferred embodiment of the invention relates to a combination such as previously defined, wherein said first antithrombin is an amino acid sequence selected from the group consisting of: SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:18, SEQ ID NO: 62, and SEQ ID NO: 64, and said second antithrombin consists of SEQ ID NO:2.

[0110] In one other particular embodiment the invention relates to a combination such as previously defined, wherein said first antithrombin is an amino acid sequence selected from the group consisting of: SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:66, and SEQ ID NO:68, and said second antithrombin consists of SEQ ID NO: 2 or SEQ ID NO:78.

[0111] Also, in another preferred embodiment, the invention relates to a combination according to the above definition, wherein said first antithrombin is chosen from the group consisting of: SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:42, SEQ ID NO:70, and SEQ ID NO:72, and said second antithrombin consists of SEQ ID NO:26.

[0112] In one other particular embodiment the invention relates to a combination such as previously defined, wherein said first antithrombin is chosen from the group consisting of: SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:44, SEQ ID NO:46, SEQ ID NO:48, SEQ ID NO:74, and SEQ ID NO:76, and said second antithrombin consists of SEQ ID NO:26 or SEQ ID NO:80.

[0113] The invention also relates to a pharmaceutical composition comprising as active ingredient at least a mutated antithrombin, as defined above, in association with a pharmaceutically acceptable vehicle, in particular a mutated antithrombin of SEQ ID NO: 62, SEQ ID NO: 64, SEQ ID NO: 66, SEQ ID NO: 68, SEQ ID NO: 70, SEQ ID NO: 72, SEQ ID NO: 74 and SEQ ID NO: 76.

[0114] By the expression "pharmaceutically acceptable vehicle", one means pharmaceutically acceptable solid or liquid, diluting or encapsulating, filling or carrying agents, which are usually employed in pharmaceutical industry for

making pharmaceutical compositions.

[0115] The dosage forms of the pharmaceutical composition includes immediate release, extended release, pulse release, variable release, controlled release, timed release, sustained release, delayed release, long acting, and combinations thereof.

5 **[0116]** Preferably, the pharmaceutical composition according to the invention can be, intravenously, intraperitoneally, subcutaneously or orally delivered.

[0117] In one other preferred embodiment, the invention relates to a pharmaceutical composition as mentioned above, said pharmaceutical composition being preferably administered at a dosage from about 80 IU/kg/day to about 300 IU/kg/day, preferably from about 100 IU/kg/day to about 200 IU/kg/day.

10 **[0118]** The invention also relates to a pharmaceutical composition, comprising as active ingredient a combination of the group comprising:

- of at least a first antithrombin consisting of one mutated antithrombin having a substantially reduced anticoagulant activity, or substantially no anticoagulant activity such as defined above, and
- 15 - at least a second antithrombin consisting of at least an antithrombin, having an anticoagulant activity similar to that of the wild type antithrombin

of the group consisting of:

- 20 - SEQ ID NO : 4; SEQ ID NO : 6, SEQ ID NO : 8 or SEQ ID NO : 10, SEQ ID NO : 18 SEQ ID NO: 62 or SEQ ID NO: 64, in association with SEQ ID NO 2,
- SEQ ID NO : 14, SEQ ID NO : 16,, SEQ ID NO : 20, SEQ ID NO : 22, SEQ ID NO : 24, SEQ ID NO: 66 or SEQ ID NO: 68, in association with SEQ ID NO 2,
- SEQ ID NO : 14, SEQ ID NO : 16,, SEQ ID NO : 20, SEQ ID NO : 22, SEQ ID NO : 24, SEQ ID NO: 66 or SEQ ID NO: 68, in association with SEQ ID NO 78,
- 25 - SEQ ID NO : 28, SEQ ID NO : 30, SEQ ID NO : 32, SEQ ID NO : 34, SEQ ID NO : 42; SEQ ID NO: 70 or SEQ ID NO: 72, in association with SEQ ID NO 26,
- SEQ ID NO : 38, SEQ ID NO : 40,, SEQ ID NO : 44, SEQ ID NO : 46, SEQ ID NO : 48, SEQ ID NO: 74 or SEQ ID NO: 76, in association with SEQ ID NO 26, and
- 30 - SEQ ID NO : 38, SEQ ID NO : 40, SEQ ID NO : 44, SEQ ID NO : 46, SEQ ID NO : 48, SEQ ID NO: 74 or SEQ ID NO: 76, in association with SEQ ID NO 80,

[0119] in association with a pharmaceutically acceptable vehicle.

35 **[0120]** Preferably, the pharmaceutical composition according to the invention can be, intravenously, intraperitoneally, subcutaneously or orally delivered.

[0121] In one other preferred embodiment, the invention relates to a pharmaceutical composition as mentioned above, said pharmaceutical composition being preferably administered at a dosage from about 20 UI/kg/day to about 600 UI/kg/day, preferably from about 40 UI/kg/day to about 300 UI/kg/day.

40 **[0122]** The invention also relates to a mutated antithrombin, which contains at least an amino acid substitution of the amino acid at position 394 of SEQ ID NO:2 by a glutamic acid (Glu) or a Glutamine (Gln), and in particular mutated antithrombin represented by SEQ ID NO: 62 or SEQ ID NO 64.

[0123] The invention also relates to a mutated antithrombin, which contains at least two mutations:

- the first mutation being, in the sequence of antithrombin represented by SEQ ID NO:2, the substitution of the amino acid at position 394, by glutamic acid (Glu) or a Glutamine (Gln), and
- 45 - the second mutation being the substitution of the amino acid at position 135, by a Glutamine (Gln),

said mutated antithrombin being in particular represented by SEQ ID NO: 66 or 68.

50 **[0124]** The invention also relates to a mutated antithrombin, which contains at least an amino acid substitution of the amino acid at position 426 of SEQ ID NO:26 by a glutamic acid (Glu) or a Glutamine (Gln), and in particular mutated antithrombin represented by SEQ ID NO: 70 or SEQ ID NO :72.

[0125] The invention also relates to a mutated antithrombin, which contains at least two mutations:

- the first mutation being, in the sequence of antithrombin represented by SEQ ID NO:26, the substitution of the amino acid at position 426, by glutamic acid (Glu) or a Glutamine (Gln), and
- 55 - the second mutation being the substitution of the amino acid at position 167, by a Glutamine (Gln),

said mutated antithrombin being in particular represented by SEQ ID NO: 74 or 76.

[0126] The invention also relates to a nucleotide sequence coding for a mutated antithrombin as defined abovesaid nucleic acid sequence being a DNA or an RNA, in particular nucleotide sequences chosen in the group consisting of SEQ ID NO: 61, SEQ ID NO: 63, SEQ ID NO: 65, SEQ ID NO: 67, SEQ ID NO: 69, SEQ ID NO: 71, SEQ ID NO: 73 and SEQ ID NO: 75, or a complementary sequence of said nucleic acid sequence.

[0127] The invention is illustrated, but not limited to, by the following example and the following figures.

FIGURES

[0128]

Figure 1 : preparation of shuttle vector carrying full length antithrombin cDNA.

2 µg of pENTR vector containing truncated AT cDNA (lane 1 and 2), pCMV6 vector containing full length AT cDNA (lane 3 and 4) or shuttle vector pENTR-AT (lane 5 and 6) are loaded on 1% agarose gel before (lane 1, 3, 5) or after (lane 2, 4, 6) complete digestion by both SacII and StuI. Molecular weight standard sizes are indicated on the left hand of the figure and expressed in base pair (bp). SacII/StuI digestion of pCMV6 vector containing full length AT cDNA releases a 1182 bp band corresponding to full length AT cDNA cloned into pENTR vector isolated from SacII/StuI digestion of pENTR vector containing truncated AT cDNA. After ligation of these two fragments the final product is effectively recircularized and shows the expected profile for pENTR-AT after SacII/StuI digestion.

Figure 2 : Characterization of the AT expression vector.

2 µg of pCDNA 3.2 vector (lane 1, 2, 3), pCDNA 3.2 vector containing full length AT cDNA (lane 4, 5, 6) or pCDNA 3.2 vector containing full length AT-N135Q-Pro394 cDNA (lane 7, 8, 9) are loaded on 1% agarose gel before endonucleases treatment (lane 1, 4, 7), after cleavage by StuI (lane 2, 5, 8), or after complete cleavage by both SacII and StuI (lane 3, 6, 9). Molecular weight standard sizes are indicated on the right hand of the figure and expressed in base pair (bp). There is one SacII and one StuI cleavage site in pCDNA 3.2 vector at position 3189 and 4329 respectively. Therefore cleavage of pCDNA 3.2 by StuI only leads to linearization of the vector (7711 bp band) whereas cleavage of pCDNA 3.2 by both StuI and SacII cuts the vector in two fragments (6571 bp and 1140 bp). Substitution of 912-3174 fragment by AT cDNA fragment (1448 bp) into pCDNA 3.2 by recombination introduces one more SacII site at position 1070 and one more StuI site at position 2252 into pCDNA-AT. Then cleavage of pCDNA-AT by StuI gives two fragments (5634bp and 1263 bp) and cleavage by both endonucleases gives 4 fragments (4452 bp, 1182 bp, 1140 and 123 bp). The same is true for -N135Q-Pro394 cDNA.

Figure 3 : Clone screening for secretion of recombinant AT in cell culture media

For each clone isolated after transfection with pCDNA-AT (clone 1 to 5 in lane 1 to 5, respectively), pCDNA-AT-N135Q (clone 1 to 4 in lane 6 to 9, respectively), or with pCDNA-AT-N135Q-Pro394 (clone 1 to 5 in lane 10 to 14, respectively), 30 µl of conditioned media harvested after 24 hours contact with cells are analysed by western-blotting in denaturing condition for their ability to secrete full length recombinant antithrombin. For each clone a single band of variable intensity corresponding to recombinant antithrombin can be seen. Recombinant wild type antithrombin migrate at the same level than control antithrombin purified from plasma (lane 15, 150 ng/lane) and expression level is estimated around 2 mg/L according to band intensity measurement. For wt-AT, clone 4 is chosen for expansion into cell factory, since the level of expression seems to be slightly higher than the others. Mutant AT-N135Q and AT-N135Q-Pro394 migrate just below control antithrombin purified from plasma (lane 15) confirming the loss of a glycosylation site due to substitution N135Q. The stable expression clones selected for large scale protein production are clones 1 for both AT-N135Q and AT-N135Q-Pro394.

Figure 4 : Integrity and purity of recombinant antithrombin.

To verify integrity and purity of recombinant antithrombin after heparin affinity purification and ion exchange concentration, 2 µg of AT-N135Q-R393H (lane 1), AT-N135Q-Pro394 (lane 2) or control plasma antithrombin (lane 3) are analyzed by SDS-PAGE followed by coomassie staining. As expected, the two mutated antithrombins migrate at molecular weight slightly lower than plasma antithrombin because of loss of a glycosylation site (substitution N135Q) and they show a single band pattern with band intensity corresponding to quantity loaded on the gel (based on absorbance estimation). Then recombinant antithrombin appears pur and can be tested for its anticoagulant properties and affinity for heparin derivatives. Molecular weight standard sizes are presented on the right hand of the figure and expressed in kiloDalton (KD).

Figure 5 : Anti-factor Xa activity of plasmatic or mutated antithrombins at saturating pentasaccharide concentration.

Figure 5A : Plasma AT (black square : 80nM, hollow square : 40nM, Black circle : 20 nM, hollow circle : 10 nM)

is tested for its ability to inhibit chromogenic substrate S2765 (200 μ M) hydrolysis by FXa (1 nM) in the presence of pentasaccharide (1 μ M or 1,73 mg/L) in continuous assay. Time expressed in second is plotted in abscissa; absorbance at 405 nm is plotted in ordinate. substrate hydrolysis curves are fitted using equation 3 to determine the kinetic rate constant (k), (gray lines)

Figure 5B: Kinetic rate constant (k) determined in figure 5 a is thus plotted as the function of AT concentration and fitted using equation 4 to determine inhibition rate constant k_{on} . The plasma antithrombin concentration (nM) is plotted in abscissa; the kinetic rate constant (k) expressed in s^{-1} is plotted in ordinate.

Figure 6 : AT-N135Q-R393H and AT-N135Q-Pro394 are tested for their ability to inhibit FXa activity in discontinuous assay. In a first time AT-N135Q-R393H (black square : 200 nM) or AT-N135Q-Pro394 (hollow square : 2,5 μ M) are incubated with FXa (20 nM) in the presence of pentasaccharide (10 μ M or 17,3 mg/L) over a period of time from 0 to 120 min (for AT-N135Q-R393H) or from 0 to 1400 min (for AT-N135Q-Pro394). In a second time FXa residual activity is measured by adding 190 μ l of S2765 (200 μ M) to 10 μ l of previous mixture. Initial rate of substrate hydrolysis is then plotted as the function of incubation time with inhibitor and curves are fitted with equation 1 to determine k_{on} (gray lines). Time expressed in minute is plotted in abscissa; substrate hydrolysis rate expressed in OD/ s^{-1} is plotted in ordinate.

Figure 7: **AT-Pro394 is tested for its ability to inhibit IL6 production by LPS stimulated blood cells.**

Blood is pre-treated for 5 minutes at 37°C with either PBS (white box), either AT-wt (Acclotline®, final concentration of 1,6 IU/ml, black box) or AT-Pro394 (final concentration of 1,6 IU/ml, gray box), and then exposed to 16 hours stimulation with 10 or 100 μ g/mL LPS. Blood is then centrifuged at 2300g for 10 minutes at 12°C and IL6 protein levels from plasma supernatants are measured quantitatively. Plasma IL6 concentration expressed in percentage is plotted in ordinate (100% corresponds to the IL6 level of the PBS control). The experience was performed with the blood of 2 different healthy subjects.

EXPERIMENTAL PART

[0129] In order to produce a mutated antithrombin having lost or reduced anticoagulant activity, in particular factor Xa and IIa inhibitory activity, and able to bind to heparin and to the pentasaccharide, different types of mutations have been contemplated and particularly, mutations within the reactive center loop (region from the amino acid 380 to amino acid 400), mutations within an exosite region remote from the loop accessible for proteinase interaction (Chuang YJ, Swanson R, Raja SM, Olson ST. Heparin enhances the specificity of antithrombin for thrombin and factor Xa independent of the reactive center loop sequence. Evidence for an exosite determinant of factor Xa specificity in heparin-activated antithrombin J Biol Chem. 2001; 276:14961-71) and mutations within a consensus sequence of glycosylation (amino acids 135 to 137 and 155 to 157) (Fan B, Crews BC, Turko IV, Choay J, Zettlmeissl G, Gettins P. Heterogeneity of recombinant human antithrombin III expressed in baby hamster kidney cells. Effect of glycosylation differences on heparin binding and structure J Biol Chem. 1993; 268:17588-96).

[0130] Several mutations have been carried out to obtain mutated antithrombins, and in particular:

- deletion within the reactive loop of the antithrombin, in the region P4- P4' (Ala 391-Asn 396) in order to eliminate antithrombin inhibitory activity toward any coagulant proteases such as FXa and FIIa,
- substitution of amino acids within the region P4-P4' (Ala 391-Asn 396) of the reactive loop, and in particular the substitution of the amino acid at position 393 (Arg) by an Histidine, or the substitution of the amino acid at position 394 (Ser) by a Glutamic acid or by a Glutamine.
- insertion of a Proline between the amino acid at position 393 and the amino acid at position 394, and
- substitution of amino acids within the region of glycosylation of the antithrombin, and in particular the substitution of the amino acid at position 135 (Asp) by a Glutamine, in order to increase the affinity with heparin and pentasaccharide.

MATERIAL AND METHODS

I/ Preparation of mutated antithrombins

Preparation of shuttle vector pENTR carrying full length antithrombin cDNA (pENTR-AT):

[0131] The antithrombin cDNA sequence initially cloned into pENTR vector (Invitrogen, HORF clone reference IOH14497) is found to be truncated and has to be replaced by the full length antithrombin sequence, cloned into pCMV6

(Origene, reference TC110831). The plasmid pCMV6 containing full length antithrombin cDNA is digested by both SacII and StuI endonucleases. The 1182 base pairs fragment is isolated on 1% agarose gel and purified using the QIAquick Gel Extraction Kit. This 1182 base pairs fragment, corresponding to the SacII-StuI fragment of antithrombin cDNA, is ligated into pENTR vector (2760 bp) also linearized by SacII and StuI and recover as described above. Result of this cassette exchange is verified by electrophoresis on 1% agarose gel (figure 1) and sequencing.

Mutagenesis on antithrombin cDNA:

[0132] The resulting plasmid pENTR carrying cDNA encoding for wild type antithrombin (pENTR-ATwt) is used as a template for further mutagenesis by PCR using the QuickChange II Site-Directed Mutagenesis Kit according to the manufacturer recommendations (Stratagene). The wild type antithrombin has the same amino acid sequence as the plasma antithrombin but is produced under a recombinant form. Mutagenic primers (table 1) are used to introduce a codon for Glutamine in place of codon for Arginine 135 (N135Q) for production of plasmid pENTR-AT-N135Q. Single amino acid substitution of Arginine 393 by an Histidine (R393H), single amino acid substitution of Serine 394 by a Glutamic acid (S394Q) or by a Glutamine (S394E), insertion of a Proline between Arginine 393 and Serine 394 (Pro394), or deletion of Arginine 393 (Δ R393), Serine 394 (Δ S394) or both Arginine 393 and Serine 394 (Δ R393S394) are introduced by PCR using the QuickChange II Site-Directed Mutagenesis Kit with pENTR-ATwt as template and mutagenic primers as described in table 1. The same couples of mutagenic primers are used in PCR reaction with pENTR-AT-N135Q as template to prepare plasmids carrying cDNA encoding for double-mutant and triple-mutant antithrombin N135Q-R393H, N135Q-S394Q, N135Q-S394E, N135Q-Pro394, N135Q- Δ R393, N135Q- Δ S394, N135Q- Δ R393S394 respectively. Then the integrity of each variant cassette that is to say cDNA encoding for the double-mutant or triple-mutant antithrombin above mentioned is established by DNA sequencing.

Cassette exchange between Shuttle vector and Expression vector:

[0133] All the cDNAs described above encoding for antithrombin, single antithrombin mutants or double antithrombin mutants are transferred from shuttle vector pENTR into eucaryote expression vector pCDNA 3.2 by recombination using Gateway LR Clonase II Enzyme Mix ("Gateway Technology" developed by Invitrogen). The final expression constructs are verified by electrophoresis on 1% agarose gel and sequencing again before transfection (figure 2).

Transfection of eucaryote cells and protein production:

[0134] Plasmid constructs resulting of previous recombination named pCDNA-ATwt, pCDNA-AT-N135Q, pCDNA-AT-R393H, pCDNA-AT-S394Q, pCDNA-AT-S394E, pCDNA-AT-Pro394, pCDNA-AT- Δ R393, pCDNA-AT- Δ S394, pCDNA-AT- Δ R393S394, pCDNA-AT-N135Q-R393H, pCDNA-AT-N135Q-S394Q, pCDNA-AT-N135Q-S394E, pCDNA-AT-N135Q-Pro394, pCDNA-AT-N135Q- Δ R393, pCDNA-AT-N135Q- Δ S394 and pCDNA-AT-N135Q- Δ R393S394, respectively are used for transfection of modified human embryonic kidney cells (HEK-293) or baby hamster kidney cells (BHK-21). Cells are grown in "Dulbecco's Modified Eagle's Medium/F-12" containing 2 mM L-Glutamine, 100 U/ml penicillin, 100 μ g/ml Streptomycin and 5 % foetal bovine serum (Invitrogen) and approximately 10^6 cells are transfected with 20 μ g of DNA by calcium-phosphate coprecipitation (Sambrook et al. Molecular cloning: A laboratory manual, 2nd edition, page 16.33). The stable expression cell lines are selected by G418 (during clones selection, G418 concentration is 0,8 mg/ml in cell culture media and then decreased to 0,4 mg/ml to maintain selection pressure during clones amplification) and screened for antithrombin secretion by ELISA, using mouse monoclonal antibody anti antithrombin as capture antibody and Horse Radish Peroxydase conjugate sheep polyclonal antibody anti antithrombin as detecting antibody (Antithrombin BioAssay™ ELISA Kit (EUROMEDEX)). The integrity of secreted antithrombin is established by western blotting using sheep monoclonal antibody anti antithrombin and Horse Radish Peroxydase conjugate donkey polyclonal antibody anti sheep (The Binding Site, UK) (figure 3). For each mutated antithrombin, a single stable expression clone is expanded into "cell factories nunclon" (Nunc) and large scale protein production is conducted with 300 μ l/cm², (as recommended by manufacturer, the minimum volume suitable for a 6320 cm² culture area cell factory is 2 liters) of « Dulbecco's Modified Eagle's Medium/F-12" containing 2 mM L-Glutamine, 100 U/ml penicillin, 100 μ g/ml Streptomycin and 5 μ g/ml Insulin/Transferrin/Selenium (Invitrogen). Conditioned media, harvested daily, are centrifuged for 15 min at 3000g at 4°C, treated with 5 mM benzamidine, 5 mM EDTA and stored at -20°C.

Protein purification:

[0135] Conditioned media are thawed, pooled, salt concentration adjusted to 0.4 M NaCl and then applied on an heparin immobilized column (Hitrap Heparin 5ml or Heparin-sepharose CL6B 50 ml, GE Biological) equilibrated with 10 mM Tris, or with 20 mM phosphate buffer, 0.4 M NaCl and 0.1 mM EDTA, pH 7.4. The bound proteins are eluted in the

same buffer with a gradient from 0.4 M to 2 M NaCl. The fractions eluted from 0.8 M NaCl and more contained only wild type antithrombin or mutated antithrombins with high heparin affinity. Mutated antithrombins carrying substitution of asparagin 135 by a glutamin (AT-N135, ATN135Q-R393H, AT-N135Q-S394Q, AT-N135Q-S394E, AT-N135Q-Pro394, AT-N135Q-ΔR393, AT-N135Q-ΔS394, AT-N135Q-ΔR393S394) are eluted from affinity column at higher ionic strength than wild type antithrombin, confirming that destruction of glycosylation site at position 135 increases affinity of antithrombin for heparin (about 90% of mutated antithrombin carrying substitution N135Q is eluted between 1 and 1,4 M NaCl compared to wild type antithrombin which 90% is eluted between 0,8 and 1,2 M NaCl). The collected fractions are pooled and the salt concentration is decreased either by over night dialysis against 10 mM Tris, or 20 mM phosphate, and 0.1 M NaCl, pH 7.4 at 4°C or applied on an HiPrep 26/10 desalting column equilibrated with 10 mM Tris, or 20 mM phosphate, and 0.1 M NaCl, pH 7.4. The antithrombin is then concentrated by ion exchange chromatography using a "Resource Q" 1ml column (GE, Biological) equilibrated with 10 mM Tris, or 20 mM phosphate, and 0.1 M NaCl, pH 7.4 and eluted in the same buffer with a NaCl gradient from 0.1 mM to 0.5 M or 20 mM to 0.5 M.

[0136] The antithrombin concentration in each elution fraction is estimated by absorbance at 280 nM with an absorption coefficient $\epsilon = 0.65 \text{ g}^{-1} \cdot \text{l} \cdot \text{cm}^{-1}$ and the integrity of purified wild type antithrombin or mutated antithrombins is tested by western blotting using the same couple of antibodies as described before, and electrophoresis on 10% acrylamide/bisacrylamide gel in native and denaturing conditions followed by coomassie brilliant blue R-250 staining (figure 4). Then, the antithrombin preparation is aliquoted and stored at -80°C before use for functional assay. The same procedure is used to purify plasma antithrombin (used as internal reference) from human plasma. Commercialized AT obtained from human plasma (Acclotine®, LFB, France) was also used as a control in the following experiments.

Table 1: oligonucleotides used for the mutated AT constructions

Sens	Mutation	Sequence	SEQ ID NO
forward	N135Q	GCCGACTCTATCGAAAAGCCCAGAAATCCTCCAAGTTAGTG	49
reverse	N135Q	CACTAACTTGGAGGATTCTGGGCTTTTCGATAGAGTCGGC	50
forward	R393H	GTTGTGATTGCTGGCCATTCGCTAAACCCCAAC	51
reverse	R393H	GTTGGGGTTTAGCGAATGGCCAGCAATCACAAC	52
forward	S394Q	GTGATTGCTGGCCGTCAGCTAAACCCCAACAGG	81
reverse	S394Q	CCTGTTGGGGTTTAGCTGACGGCCAGCAATCAC	82
forward	S394E	GTGATTGCTGGCCGTGAGCTAAACCCCAACAGG	83
reverse	S394E	CCTGTTGGGGTTTAGCTCAGGCCAGCAATCAC	84
forward	Pro394	GTTGTGATTGCTGGCCGTCCATCGCTAAACCCCAAC	53
reverse	Pro394	GTTGGGGTTTAGCGATGGACGGCCAGCAATCACAAC	54
forward	ΔR393-S394	GCTGTTGTGATTGCTGGCCTAAACCCCAACAGGGTG	55
reverse	ΔR393-S394	CACCCTGTTGGGGTTTAGGCCAGCAATCACAACAGC	56
forward	ΔR393	CTGTTGTGATTGCTGGCTCGCTAAACCCCAACAG	57
reverse	ΔR393	CTGTTGGGGTTTAGCGAGCCAGCAATCACAACAG	58
forward	ΔS394	TGTGATTGCTGGCCGTCTAAACCCCAACAGGG	59
reverse	ΔS394	CCCTGTTGGGGTTTAGACGGCCAGCAATCACA	60

II/ In vitro characterization of the mutated antithrombins

[0137] Characterization of the mutated antithrombins aims at

- a) demonstrating that, in a purified system, the following mutated antithrombins: AT-R393H, S394Q, AT-S394E, AT-Pro394, AT-ΔR393-S394, AT-ΔR393, AT-ΔS394, AT-N135Q-R393H, AT-N135Q-S394Q, AT-N135Q-S394E, AT-N135Q-Pro394, AT-N135Q-ΔR393-S394, AT-N135Q-ΔR393 and AT-N135Q-ΔS394 exhibit a reduced anti FXa and anti FIIa activity compared with that of wild type antithrombin (AT-wt) in the presence or absence of heparin's derivatives.
- b) demonstrating that, the following mutated antithrombins AT-R393H, AT-S394Q, AT-S394E, AT-Pro394, AT-ΔR393-S394, AT-ΔR393, AT-ΔS394, AT-N135Q-R393H, AT-N135Q-S394Q, AT-N135Q-S394E, AT-N135Q-Pro394,

AT-N135Q-ΔR393-S394, AT-N135Q-ΔR393, AT-N135Q-ΔS394, or a composition comprising at least one of these mutated antithrombins and an antithrombin having an anticoagulant activity similar to that of the wild type antithrombin, have, at least, equivalent cytoprotective properties when compared to wild type antithrombin.

a) Anti factor Xa inhibitory activity of the mutated antithrombins in a purified system

[0138] The kinetic assays for antithrombin inhibition of factor Xa (FXa, Kordia) are performed in 'kinetic' buffer (Hepes, 20 mM phosphate, pH 7,4, 0,15 M NaCl, 0,1% PEG 8000 and 1 mg/ml bovine serum albumin) in pseudo first order conditions. Briefly, factor Xa is incubated with an excess of tested antithrombins (corresponding to plasma antithrombin, or wild type antithrombin or mutated antithrombins and varying in each assay realized) in the presence or absence of pentasaccharide (Fondaparinux sodique, Arixtra®, GlaxoSmithKline) and the factor Xa residual activity is measured as a function of time. The pentasaccharide is added in excess in the reaction media so that every tested antithrombin is bound to the pentasaccharide. In the absence of pentasaccharide, polybrene (100 µg/ml final) is added in order to neutralize any sulfated glycosaminoglycan that may be present in the reaction media. The residual factor Xa activity is measured as the increase in absorbance at 405 nm resulting from cleavage of the chromogenic substrate (S2765 or S2222, Chromogenix) using a microplate reader (Dynatech MR 5000). The analysis of the data is performed using the GraphPad Prism version 3 software. Absorbance recording is continuous or discontinuous according to the expected inhibition rate constant (kon).

[0139] The inhibition rate constant (kon) is the second order rate constant given in M⁻¹.s⁻¹ which define the velocity of stable complex formation between protease and antithrombin (higher is the kon value, faster will the complex be established).

[0140] When the expected kon is lower than 10⁴ M⁻¹.s⁻¹ the discontinuous method is used. Factor Xa (2 to 200 nM) is incubated with tested antithrombins (20 nM to 20 µM) in the presence of pentasaccharide or polybrene in a final volume of 10 µl for 10 seconds to 5 hours, or 10 seconds to 24 hours. At the end of this incubation period, 190 µl of kinetic buffer containing 200 µM substrate is added and absorbance at 405 nm is recorded.

[0141] The kinetic rate constant (k) is estimated by fitting the substrate hydrolysis initial rate curve to equation (1) using non-linear regression with v0 and v∞ being the substrate hydrolysis rate at time t0 or t∞ respectively.

$$v_t = (v_0 + v_{\infty}) \cdot \exp(-k \cdot t) \quad (1)$$

[0142] The inhibition rate constant (kon) is calculated from the rate constant (k) using equation (2) where AT is the tested antithrombin concentration.

$$k = AT \cdot kon \quad (2)$$

[0143] When the expected kon is higher than 10⁴ M⁻¹.s⁻¹, the continuous method is used. The tested antithrombin (1 nM to 1 µM), is incubated with the substrate (200 µM), in the presence of pentasaccharide or polybrene in a final volume of 190 µl and the reaction is started by addition of 10 µl. of factor Xa (2 to 200 nM). The rate constant (k) is obtained by fitting the substrate hydrolysis curve to equation (3) or (3') using non-linear regression analysis where A0 is the absorbance at t0, and vi and vs are respectively the initial and final rates of substrate hydrolysis in the absence of tested antithrombin.

$$A_{405} = A_0 + v_i \cdot (1 - \exp(-k \cdot t)) / k \quad (3)$$

Equation (3') is also used, particularly in presence of plasma.

$$A_{405} = A_0 + v_s \cdot t + (v_i - v_s) \cdot (1 - \exp(-k \cdot t)) / k$$

[0144] The inhibition rate constant (kon) is calculated from the kinetic constant (k) using equation (4) that takes into account the competitive effect of the substrate, with S being the initial substrate concentration, Km, the Michaelis constant for factor Xa-substrate interaction, AT the tested antithrombin concentration.

$$k = (kon / (1 + S / K_m)) \cdot [AT] \quad (4)$$

[0145] Mutated antithrombins and wild type AT inhibitory activity are measured in the same conditions and compared with plasma AT inhibitory activity.

[0146] The results with or without pentasaccharide are :

- wild type antithrombin and AT-N135Q factor Xa inhibitory activity is similar to plasma antithrombin factor Xa inhibitory activity,
- factor Xa inhibitory activity of the following mutated antithrombins : AT-R393H, AT-Pro394, AT-ΔR393-S394, AT-ΔR393, AT-ΔS394, AT-N135Q-R393H, AT-N135Q-Pro394, AT-N135Q-ΔR393-S394, AT-N135Q-ΔR393, AT-N135Q-ΔS394, is negligible compared with wild type antithrombin factor Xa inhibitory activity.
- factor Xa inhibitory activity of the following mutated antithrombins : AT-S394Q, AT-S394E, AT-N135Q-S394Q and AT-N135Q-S394E, is 2 to 20 fold decreased compared with wild type antithrombin factor Xa inhibitory activity.
- A decrease in factor Xa inhibitory activity from 2 to 20 fold compared with wild type antithrombin is reached with a composition containing one of the following mutated antithrombins : AT-R393H, AT-S394Q, AT-S394E, AT-Pro394, AT-ΔR393-S394, AT-ΔR393, AT-ΔS394, AT-N135Q-R393H, AT-N135Q-S394Q, AT-N135Q-S394E, AT-N135Q-Pro394, AT-N135Q-ΔR393-S394, AT-N135Q-ΔR393, or AT-N135Q-ΔS394, and AT-wt or AT-N135Q, in a varying ratio.

[0147] For example, inhibition rate constant (k_{on}) of plasma AT for factor Xa in the presence of saturating amount of pentasaccharide is estimated using continuous method (figure 5 a and 5 b). A value of $2.52 \times 10^5 \text{ M}^{-1} \cdot \text{s}^{-1}$ is found which is comparable to published values (Olson ST, Björk I, Sheffer R, Craig PA, Shore JD, Choay J., J Biol Chem. 1992 Jun 25; 267 (18) : 12528-38, "Role of the antithrombin-binding pentasaccharide in heparin acceleration of antithrombin-proteinase reactions. Resolution of the antithrombin conformational change contribution to heparin rate enhancement.) Using this method AT-N135Q-R393H and AT-N135Q-Pro394 are found to be slow factor Xa inhibitors, even in the presence of saturating pentasaccharide concentration. Thus, discontinuous method was performed to evaluate k_{on} values for factor Xa inhibition by AT-N135Q-R393H and AT-N135Q-Pro394 in the presence of pentasaccharide (figure 6). AT-N135Q-R393H anticoagulant activity is largely reduced whereas AT-N135Q-Pro394 is almost devoided of anti-factor Xa activity. AT-N135Q-R393H and AT-N135Q-Pro394 k_{on} values are estimated at $4415 \text{ M}^{-1} \cdot \text{s}^{-1}$ and $33 \text{ M}^{-1} \cdot \text{s}^{-1}$, respectively, which is 95 times and at least 7600 times lower than plasma AT.

b) Anti factor IIa inhibitory activity of the mutated antithrombins in a purified system.

[0148] The kinetic assays for antithrombin inhibition of factor IIa (FIIa, Kordia) are performed in 'kinetic' buffer (Hepes, 20 mM phosphate, pH 7,4, 0,15 M NaCl, 0,1% PEG 8000 and 1 mg/ml bovine serum albumin) in pseudo first order conditions. Briefly, factor IIa is incubated with an excess of tested antithrombins (corresponding to plasma antithrombin, or wild type antithrombin or mutated antithrombins and varying in each assay realized) in the presence or absence of heparin (heparin sodium, Choay®) and the factor IIa residual activity is measured as a function of time. Heparin is added in excess in the reaction media so that every tested antithrombin is bound to heparin. In the absence of heparin, polybrene (100 $\mu\text{g/ml}$ final) is added in order to neutralize any sulfated glycosaminoglycan that may be present in the reaction media. The residual factor IIa activity is measured as the increase in absorbance at 405 nm resulting from cleavage of the chromogenic substrate (S2238, Chromogenix) using a microplate reader (Dynatech MR 5000). The analysis of the data is performed using the GraphPad Prism version 3 software. Absorbance recording is continuous or discontinuous according to the expected inhibition rate constant (k_{on}).

[0149] The inhibition rate constant (k_{on}) is the second order rate constant given in $\text{M}^{-1} \cdot \text{s}^{-1}$ which define the velocity of stable complex formation between protease and antithrombin (higher is the k_{on} value, faster will the complex be established).

[0150] When the expected k_{on} is lower than $10^4 \text{ M}^{-1} \cdot \text{s}^{-1}$ the discontinuous method is used. Factor IIa (2 to 200 nM) is incubated with tested antithrombins (20 nM to 20 μM), in the presence of heparin or polybrene in a final volume of 10 μl for 10 seconds to 5 hours, or 10 seconds to 24 hours. At the end of this incubation period, 190 μl of kinetic buffer containing 200 μM substrate is added and absorbance at 405 nm is recorded.

[0151] The kinetic rate constant (k) is estimated by fitting the substrate hydrolysis initial rate curve to equation (1) using non-linear regression with v_0 and v_{∞} being the substrate hydrolysis rate at time 0 or too respectively.

$$v_t = (v_0 + v_{\infty}) \cdot \exp(-k \cdot t) \quad (1)$$

[0152] The inhibition rate constant (k_{on}) is calculated from the rate constant (k) using equation (2) where AT is the tested antithrombin concentration.

$$k = AT \cdot k_{on} \quad (2)$$

[0153] When the expected k_{on} is higher than $10^4 \text{ M}^{-1} \cdot \text{s}^{-1}$, the continuous method is used. The tested antithrombin (1 nM to 1 μM), is incubated with the substrate (200 μM), in the presence of heparin or polybrene in a final volume of 190 μL and the reaction is started by addition of 10 μL of factor IIa (2 to 200 nM). The rate constant (k) is obtained by fitting the substrate hydrolysis curve to equation (3) or (3') using non-linear regression analysis where A_0 is the absorbance at t_0 , and v_i and v_s are respectively the initial and final rates of substrate hydrolysis in the absence of tested antithrombin.

$$A_{405} = A_0 + v_i(1 - \exp(-k \cdot t)) / k \quad (3)$$

$$A_{405} = A_0 + v_s \cdot t + (v_i - v_s) \cdot (1 - \exp(-k \cdot t)) / k \quad (3')$$

[0154] The inhibition rate constant (k_{on}) is calculated from the kinetic constant (k) using equation (4) that takes into account the competitive effect of the substrate, with S being the initial substrate concentration, K_m , the Michaelis constant for factor IIa-substrate interaction, AT the tested antithrombin concentration.

$$k = (k_{on} / (1 + S / K_m)) \cdot [AT] \quad (4)$$

[0155] Mutated antithrombins and wild type AT inhibitory activity are measured in the same conditions and compared with plasma AT inhibitory activity.

[0156] The results with or without heparin are :

- wild type antithrombin and AT-N135Q factor IIa inhibitory activity is similar to plasma antithrombin factor IIa inhibitory activity,
- factor IIa inhibitory activity of the following mutated antithrombins : AT-R393H, AT-Pro394, AT- Δ R393-S394, AT- Δ R393, AT- Δ S394, AT-N135Q-R393H, AT-N135Q-Pro394, AT-N135Q- Δ R393-S394, AT-N135Q- Δ R393, AT-N135Q- Δ S394, is negligible compared with wild type antithrombin factor IIa inhibitory activity.
- factor IIa inhibitory activity of the following mutated antithrombins : AT-S394Q, AT-S394E, AT-N135Q-S394Q and AT-N135Q-S394E, is 2 to 20 fold decreased compared with wild type antithrombin factor IIa inhibitory activity.
- A decrease in factor IIa inhibitory activity from 2 to 20 fold compared with wild type antithrombin is reached with a composition containing one of the following mutated antithrombins : AT-R393H, AT-S394Q, AT-S394E, AT-Pro394, AT- Δ R393-S394, AT- Δ R393, AT- Δ S394, AT-N135Q-R393H, AT-N135Q-S394Q, AT-N135Q-S394E, AT-N135Q-Pro394, AT-N135Q- Δ R393-S394, AT-N135Q- Δ R393, or AT-N135Q- Δ S394, and AT-wt or AT-N135Q, in a varying ratio.

c) In vitro evaluation of cytoprotective properties of the mutated antithrombins

c-1) Evaluation on human whole blood

[0157] Cytoprotective properties of mutated antithrombins (AT-R393H, AT-S394Q, AT-S394E, AT-Pro394, AT- Δ R393-S394, AT- Δ R393, AT- Δ S394, AT-N135Q-R393H, AT-N135Q-S394Q, AT-N135Q-S394E, AT-N135Q-Pro394, AT-N135Q- Δ R393-S394, AT-N135Q- Δ R393 and AT-N135Q- Δ S394) are evaluated, *in vitro*, on human whole blood exposed to bacterial lipopolysaccharide (LPS).

[0158] Venous blood was collected into tubes containing 0.11 mol/L trisodium citrate (1:10). Blood is either untreated or pre-treated with different concentration ranging from 1 to 10 IU/mL of wild type or mutated AT for 5 or 30 minutes at 37°C, and then exposed to 5 or 16 hours stimulation with 10, 50 or 100 $\mu\text{g/mL}$ LPS. Blood is then centrifuged at 2300g for 10 minutes at 12°C and plasma supernatants stored at -80°C until use. IL6 and $\text{TNF}\alpha$ protein levels from plasma supernatants are measured quantitatively using a commercially available enzyme-linked immunosorbent assay (ELISA) (IL-6 duoset and $\text{TNF}\alpha$ duoset, R&D System, Minneapolis, MI, USA)

[0159] In the condition of the assay, addition of AT-R393H, AT-S394Q, AT-S394E, AT-Pro394, AT- Δ R393-S394, AT- Δ R393, AT- Δ S394, AT-N135Q-R393H, AT-N135Q-Pro394, AT-N135Q- Δ R393-S394, AT-N135Q- Δ R393, AT-N135Q- Δ S394, or a composition comprising at least one of these AT variants with AT-wt or AT-N135Q, produces a significant decrease in IL6 and $\text{TNF}\alpha$ levels in blood samples.

c-2) Evaluation on murine mixed cortical cultures

[0160] Culturing of primary cells is performed as described (Lubetzki, C., Demerens, C., Anglade, P., Villarroya, H., Frankfurter, A., Lee, V.M.Y., Zalc, B., 1993. Proc. Natl. Acad. Sci. U. S. A. 90, 6820 - 6824. « Even in culture, oligodendrocytes myelinate solely axons ») by using brain tissue from embryos isolated from mice at 16 days post-coitum. Cerebral hemispheres are dissected from embryo brains, dissociated via trypsin digestion and the single cell suspension is seeded at 10^5 cells in 200 μ l medium per well onto BioCoat® poly-L-lysine coated 96-well plates (Becton Dickinson, Bedford, MA 01730, USA). Cells are cultured in Bottenstein-Sato medium (GIBCO Invitrogen), supplemented with 1% FCS, 1% penicillin - streptomycin solution (Seromed) and recombinant platelet-derived growth factor AA (PDGF-AA, R&D Systems) at 10 ng/mL. Cultures are grown at 37 °C and 10% CO₂ for several weeks.

LPS stimulation

[0161] Cells are either untreated or pre-treated with various concentrations ranging from 1 to 10 IU/ml of wild type or mutated AT for 3 hours and are incubated for 48 hours with 10 ng/ml of LPS, at 37°C and 10% CO₂. Cell supernatants are then centrifuged at 2300g for 10 minutes at 12°C and stored at -80°C until use. IL6 and TNF α protein levels from cell supernatants are measured quantitatively using a commercially available enzyme-linked immunosorbent assay (ELISA) (IL-6 duoset and TNF α duoset, R&D System, Minneapolis, MI, USA)

[0162] In the condition of the assay, addition of AT-R393H, AT-S394Q, AT-S394E, AT-Pro394, AT- Δ R393-S394, AT- Δ R393, AT- Δ S394, AT-N135Q-R393H, AT-N135Q-Pro394, AT-N135Q- Δ R393-S394, AT-N135Q- Δ R393, AT-N135Q- Δ S394, or a composition comprising at least one of these AT variants with AT-wt or AT-N135Q, produces a significant decrease in IL6 and TNF α levels in cell culture supernatant.

Oxygen-glucose deprivation (OGD)

[0163] To induce hypoxia/reoxygenation injury, oxygen-glucose deprivation (OGD) experiments were done by treatment for 1 to 12 hours with 95% N₂/5% CO₂ in serum-free DMEM without glucose, followed by 12 to 24 hours of exposure to normoxic conditions with 5 mmol/L glucose. Wild type or mutated AT (concentration ranging from 1 to 10 IU/mL) was added throughout the entire time of the study (13 to 36 hours).

[0164] Cell damage was evaluated by measuring the amount of lactate dehydrogenase (LDH) released from injured cells into the extracellular fluid 24 hours after exposure to OGD. Background LDH release was determined in control cultures not exposed to OGD and was subtracted from all experimental values

[0165] In the condition of the assay, addition of AT-R393H, AT-S394Q, AT-S394E, AT-Pro394, AT- Δ R393-S394, AT- Δ R393, AT- Δ S394, AT-N135Q-R393H, AT-N135Q-Pro394, AT-N135Q- Δ R393-S394, AT-N135Q- Δ R393, AT-N135Q- Δ S394, or a composition comprising at least one of these AT variants with AT-wt or AT-N135Q, produces a significant decrease in LDH release from injured cells into the extracellular fluid.

III/ In vivo evaluation of Cytoprotective properties of the mutated antithrombins

[0166] The efficiency of the mutated antithrombins AT-R393H, AT-Pro394, AT- Δ R393-S394, AT- Δ R393, AT- Δ S394, AT-N135Q-R393H, AT-N135Q-S394Q, AT-N135Q-S394E, AT-N135Q-Pro394, AT-N135Q- Δ R393-S394, AT-N135Q- Δ R393, AT-N135Q- Δ S394 as antidotes is evaluated in a murine model.

a) Animals

[0167] Wild-type C57BL/6 male mice, at least 12-week-old (JANVIER) are anesthetized using a protocol that does not modify the coagulation parameters, and in accordance with the European guidelines for animal experimentation.

[0168] In all experiments, antithrombin variant or placebo is administrated by intra-venous injection in the caudal vein.

[0169] The blood is collected by puncture in cave vein into tubes containing 0.105 mol/L trisodium citrate (1:10). Platelet-poor plasma is obtained by centrifugation at 2300g for 10 minutes at 12°C and stored at -80°C until use.

b) Experimental protocol

[0170] Mouse experiments are performed to assess each antithrombin variant against placebo in two sepsis models: 1) cecum ligation and puncture (CLP), 2) lipopolysaccharide (LPS) injection. For each antithrombin variant, a first set of experiment compares inflammatory and coagulant response to sepsis with the placebo in both sepsis models. In a second set of experiment, survival after CLP and LPS injection is compared between antithrombin injected-mice and placebo-injected mice. Housing and experiments are in accordance with French regulations and European Community

experimental guidelines.

1- Sepsis models

[0171] The CLP procedure is performed as described elsewhere (Wichterman KA, Baue AE, Chaudry IH. Sepsis and septic shock - a review of laboratory models and a proposal. J Surg Res 1980; 29: 189-201). Briefly, under isoflurane anesthesia the abdominal wall is opened through a 1-cm midline incision. The cecum is exposed and ligated about 15 mm proximal to the cecal pole with 5/0 Prolene thread (Ethicon, Somerville, NJ, USA), without stricture of the ileocecal valve. The ligated cecum is then punctured once with a 21-gauge needle. The cecum is gently pressed until a small drop of stool appeared; 1 ml of 0.9% normal saline is injected into the peritoneal cavity just before abdominal closure in sham and CLP animals. No further resuscitation is performed and no antibiotics are administered. The abdominal wall are then closed (two layers, muscle and skin; 5/0 Ethilon thread). As a control, sham surgery is performed according to the CLP procedure except that the cecum is neither ligated nor punctured.

[0172] In the LPS sepsis model, LPS injection (5 or 10 mg/kg) is realized intraperitoneously. Control animals will be injected with the solvent only.

[0173] In both models, AT is administrated by intra-venous injection in the caudal vein at a dose from about 40 to about 300 IU/kg/day.

2- Survival analyses

[0174] For each antithrombin variant to be tested 2 groups of 15 mice each are used for CLP sepsis model:

- In the first group mice receive antithrombin variant and are subjected to CLP.
- In the second group, mice receive placebo and are subjected to CLP.

[0175] For each antithrombin variant to be tested 2 groups of 10 mice each are used for LPS sepsis model:

- In the first group mice receive antithrombin variant and are injected with LPS.
- In the second group, mice receive placebo and are injected with solvent.

[0176] All paired mice undergo surgery or injection on the same days. Post-operative or post-LPS injection survival is assessed every 2 hours for 48 hours and then every 8 hours until all mice have died.

[0177] In these experimental conditions, a longer survival in antithrombin variants-injected mice in comparison with placebo-injected mice is observed.

3- Evaluation of inflammatory and coagulant response

[0178] For each antithrombin variant to be tested, 4 groups of 5 mice each are used for each sepsis model:

CLP model:

[0179]

- In the first group, mice receive antithrombin variant and are subjected to CLP.
- In the second group, mice receive placebo and are subjected to CLP.
- In the third group, mice receive antithrombin variant and are sham-operated.
- In the last group, mice receive placebo and are sham-operated.

LPS model:

[0180]

- In the first group, mice receive antithrombin variant and are injected with LPS.
- In the second group, mice receive placebo and are injected with LPS.
- In the third group, mice receive antithrombin variant and are injected with solvent.
- In the last group, mice receive placebo and are injected with solvent.

[0181] Blood is sampled 1 week preoperatively and at 16 hours post surgery.

[0182] Influence of mutated AT administration on bleeding tendency is evaluated by examination of the abdominal cavity in Sham and CLP operated mice after sacrifice following postoperative blood sampling.

[0183] Antithrombin antigen levels are measured using an ELISA test (Antithrombin BioAssay™ ELISA Kit (EUROME-DEX), and antithrombin factor Xa inhibitory activity in mice's plasma is determined using the Biophen® AT kit (Hyphen BiMed, France). Inflammatory and procoagulant response to sepsis in mice injected with the antithrombin variants is evaluated by measurement of several parameters. Leukocyte, and platelet counts and hemoglobin level determinations are automated (Sci Vet ABC Animal Blood Counter, ABX Diagnostics, Montpellier, France). Plasma interleukin-6 (IL-6) and TNF α concentrations are assessed with the mouse IL-6 and TNF α Quantikine kits (R&D Systems, Minneapolis, MI, USA). Coagulation activation is evaluated by F1+2 measurement.

[0184] Moreover, intravascular fibrin depositions are also assessed immunohistochemically using polyclonal antibodies to fibrinogen. Fibrinogen/fibrin-bound antibodies are detected with direct immunofluorescence. Sections treated without primary antibodies serve as negative controls.

[0185] Using these experimental conditions, we observed a diminished inflammatory and procoagulant response to sepsis in mice injected with the antithrombin variants in comparison with placebo-injected mice. Notably, a lower IL-6 and TNF α concentrations, a reduced decline in platelet and leukocyte count, a lower thrombin generation evidenced by lower F1+2 fragments, reduced fibrin deposition in the kidneys. AT variants administration results in a 1 to 7.5 fold increase in AT circulating antigen levels.

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<120> MUTATED ANTITHROMBINS, A PROCESS FOR PREPARING THE SAME AND THEIR USE AS DRUGS

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Gly Ile Val Ala Glu Gly Arg Asp Asp Leu Tyr Val Ser Asp Ala Phe
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5 His Lys Ala Phe Leu Glu Val Asn Glu Glu Gly Ser Glu Ala Ala Ala
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10 Ser Thr Ala Val Val Ile Ala Gly Arg Ser Leu Asn Pro Asn Arg Val
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His Leu Ala Asp Ser Lys Asn Asp Asn Asp Asn Ile Phe Leu Ser Pro
65 70 75 80

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Leu Ser Ile Ser Thr Ala Phe Ala Met Thr Lys Leu Gly Ala Cys Asn
85 90 95

55 gac acc ctc cag caa ctg atg gag gta ttt aag ttt gac acc ata tct 336
Asp Thr Leu Gln Gln Leu Met Glu Val Phe Lys Phe Asp Thr Ile Ser
100 105 110

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	Ser Thr Ala Val Val Ile Ala Gly His Ser Leu Asn Pro Asn Arg Val	
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15	act ttc aag gcc aac agg cct ttc ctg gtt ttt ata aga gaa gtt cct	1248
	Thr Phe Lys Ala Asn Arg Pro Phe Leu Val Phe Ile Arg Glu Val Pro	
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20	ctg aac act att atc ttc atg ggc aga gta gcc aac cct tgt gtt aag	1296
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10	Asp	Glu	Gly	Ser	Glu	Gln	Lys	Ile	Pro	Glu	Ala	Thr	Asn	Arg	Arg	Val
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15	Trp	Glu	Leu	Ser	Lys	Ala	Asn	Ser	Arg	Phe	Ala	Thr	Thr	Phe	Tyr	Gln
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30	Asp	Thr	Leu	Gln	Gln	Leu	Met	Glu	Val	Phe	Lys	Phe	Asp	Thr	Ile	Ser
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40																
45																
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25	Lys	Thr	Glu	Gly	Arg	Ile	Thr	Asp	Val	Ile	Pro	Ser	Glu	Ala	Ile	Asn	
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55	Glu	Lys	Ser	Leu	Ala	Lys	Val	Glu	Lys	Glu	Leu	Thr	Pro	Glu	Val	Leu	
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Gly Ile Val Ala Glu Gly Arg Asp Asp Leu Tyr Val Ser Asp Ala Phe
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5 His Lys Ala Phe Leu Glu Val Asn Glu Glu Gly Ser Glu Ala Ala Ala
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10 Ser Thr Ala Val Val Ile Ala Gly His Ser Leu Asn Pro Asn Arg Val
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15 Thr Phe Lys Ala Asn Arg Pro Phe Leu Val Phe Ile Arg Glu Val Pro
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atg aat ccc atg tgc att tac cgc tcc ccg gag aag aag gca act gag 96
Met Asn Pro Met Cys Ile Tyr Arg Ser Pro Glu Lys Lys Ala Thr Glu
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40 gat gag ggc tca gaa cag aag atc ccg gag gcc acc aac cgg cgt gtc 144
Asp Glu Gly Ser Glu Gln Lys Ile Pro Glu Ala Thr Asn Arg Arg Val
35 40 45

45 tgg gaa ctg tcc aag gcc aat tcc cgc ttt gct acc act ttc tat cag 192
Trp Glu Leu Ser Lys Ala Asn Ser Arg Phe Ala Thr Thr Phe Tyr Gln
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50 cac ctg gca gat tcc aag aat gac aat gat aac att ttc ctg tca ccc 240
His Leu Ala Asp Ser Lys Asn Asp Asn Asp Asn Ile Phe Leu Ser Pro
65 70 75 80

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Leu Ser Ile Ser Thr Ala Phe Ala Met Thr Lys Leu Gly Ala Cys Asn
85 90 95

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100 105 110

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5	cat aag gca ttt ctt gag gta aat gaa gaa ggc agt gaa gca gct gca	1152
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	Ser Thr Ala Val Val Ile Ala Gly Arg Pro Ser Leu Asn Pro Asn Arg	
	385 390 395 400	
15	gtg act ttc aag gcc aac agg cct ttc ctg gtt ttt ata aga gaa gtt	1248
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20	cct ctg aac act att atc ttc atg ggc aga gta gcc aac cct tgt gtt	1296
	Pro Leu Asn Thr Ile Ile Phe Met Gly Arg Val Ala Asn Pro Cys Val	
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10 Asp Glu Gly Ser Glu Gln Lys Ile Pro Glu Ala Thr Asn Arg Arg Val
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15 Trp Glu Leu Ser Lys Ala Asn Ser Arg Phe Ala Thr Thr Phe Tyr Gln
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20 His Leu Ala Asp Ser Lys Asn Asp Asn Asp Asn Ile Phe Leu Ser Pro
65 70 75 80

25 Leu Ser Ile Ser Thr Ala Phe Ala Met Thr Lys Leu Gly Ala Cys Asn
85 90 95

30 Asp Thr Leu Gln Gln Leu Met Glu Val Phe Lys Phe Asp Thr Ile Ser
100 105 110

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70	Asp	Met	Gly	Leu	Val	Asp	Leu	Phe	Ser	Pro	Glu	Lys	Ser	Lys	Leu	Pro	
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Gly Ile Val Ala Glu Gly Arg Asp Asp Leu Tyr Val Ser Asp Ala Phe
355 360 365

5 His Lys Ala Phe Leu Glu Val Asn Glu Glu Gly Ser Glu Ala Ala Ala
370 375 380

10 Ser Thr Ala Val Val Ile Ala Gly Arg Pro Ser Leu Asn Pro Asn Arg
385 390 395 400

15 Val Thr Phe Lys Ala Asn Arg Pro Phe Leu Val Phe Ile Arg Glu Val
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	Met	Asn	Pro	Met	Cys	Ile	Tyr	Arg	Ser	Pro	Glu	Lys	Lys	Ala	Thr	Glu	
				20					25					30			
10	gat	gag	ggc	tca	gaa	cag	aag	atc	ccg	gag	gcc	acc	aac	cgg	cgt	gtc	144
	Asp	Glu	Gly	Ser	Glu	Gln	Lys	Ile	Pro	Glu	Ala	Thr	Asn	Arg	Arg	Val	
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	Trp	Glu	Leu	Ser	Lys	Ala	Asn	Ser	Arg	Phe	Ala	Thr	Thr	Phe	Tyr	Gln	
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	His	Leu	Ala	Asp	Ser	Lys	Asn	Asp	Asn	Asp	Asn	Ile	Phe	Leu	Ser	Pro	
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25	ctg	agt	atc	tcc	acg	gct	ttt	gct	atg	acc	aag	ctg	ggg	gcc	tgt	aat	288
	Leu	Ser	Ile	Ser	Thr	Ala	Phe	Ala	Met	Thr	Lys	Leu	Gly	Ala	Cys	Asn	
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5		gag	aaa	aca	tct	gat	cag	atc	cac	ttc	ttc	ttt	gcc	aaa	ctg	aac	tgc	384
		Glu	Lys	Thr	Ser	Asp	Gln	Ile	His	Phe	Phe	Phe	Ala	Lys	Leu	Asn	Cys	
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10		Arg	Leu	Tyr	Arg	Lys	Ala	Asn	Lys	Ser	Ser	Lys	Leu	Val	Ser	Ala	Asn	
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15		Arg	Leu	Phe	Gly	Asp	Lys	Ser	Leu	Thr	Phe	Asn	Glu	Thr	Tyr	Gln	Asp	
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		Ile	Ser	Glu	Leu	Val	Tyr	Gly	Ala	Lys	Leu	Gln	Pro	Leu	Asp	Phe	Lys	
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		Glu	Asn	Ala	Glu	Gln	Ser	Arg	Ala	Ala	Ile	Asn	Lys	Trp	Val	Ser	Asn	
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30		Glu	Leu	Thr	Val	Leu	Val	Leu	Val	Asn	Thr	Ile	Tyr	Phe	Lys	Gly	Leu	
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35		aag	gct	gat	gga	gag	tcg	tgt	tca	gca	tct	atg	atg	tac	cag	gaa	ggc	768
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40		Lys	Phe	Arg	Tyr	Arg	Arg	Val	Ala	Glu	Gly	Thr	Gln	Val	Leu	Glu	Leu	
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45		Pro	Phe	Lys	Gly	Asp	Asp	Ile	Thr	Met	Val	Leu	Ile	Leu	Pro	Lys	Pro	
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		Glu	Lys	Ser	Leu	Ala	Lys	Val	Glu	Lys	Glu	Leu	Thr	Pro	Glu	Val	Leu	
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		ccc	cgc	ttc	cgc	att	gag	gac	ggc	ttc	agt	ttg	aag	gag	cag	ctg	caa	1008
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5	ggt att gtt gca gaa ggc cga gat gac ctc tat gtc tca gat gca ttc	1104
	Gly Ile Val Ala Glu Gly Arg Asp Asp Leu Tyr Val Ser Asp Ala Phe	
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	His Lys Ala Phe Leu Glu Val Asn Glu Glu Gly Ser Glu Ala Ala Ala	
	370 375 380	
15	agt acc gct gtt gtg att gct ggc tcg cta aac ccc aac agg gtg act	1200
	Ser Thr Ala Val Val Ile Ala Gly Ser Leu Asn Pro Asn Arg Val Thr	
	385 390 395 400	
20	ttc aag gcc aac agg cct ttc ctg gtt ttt ata aga gaa gtt cct ctg	1248
	Phe Lys Ala Asn Arg Pro Phe Leu Val Phe Ile Arg Glu Val Pro Leu	
	405 410 415	
25	aac act att atc ttc atg ggc aga gta gcc aac cct tgt gtt aag	1293
	Asn Thr Ile Ile Phe Met Gly Arg Val Ala Asn Pro Cys Val Lys	
	420 425 430	
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5 Met Asn Pro Met Cys Ile Tyr Arg Ser Pro Glu Lys Lys Ala Thr Glu
20 25 30

10 Asp Glu Gly Ser Glu Gln Lys Ile Pro Glu Ala Thr Asn Arg Arg Val
35 40 45

15 Trp Glu Leu Ser Lys Ala Asn Ser Arg Phe Ala Thr Thr Phe Tyr Gln
50 55 60

20 His Leu Ala Asp Ser Lys Asn Asp Asn Asp Asn Ile Phe Leu Ser Pro
65 70 75 80

25 Leu Ser Ile Ser Thr Ala Phe Ala Met Thr Lys Leu Gly Ala Cys Asn
85 90 95

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	Asp	Thr	Leu	Gln	Gln	Leu	Met	Glu	Val	Phe	Lys	Phe	Asp	Thr	Ile	Ser	
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				115				120					125				
10	Arg	Leu	Tyr	Arg	Lys	Ala	Asn	Lys	Ser	Ser	Lys	Leu	Val	Ser	Ala	Asn	
		130					135					140					
15	Arg	Leu	Phe	Gly	Asp	Lys	Ser	Leu	Thr	Phe	Asn	Glu	Thr	Tyr	Gln	Asp	
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25	Glu	Asn	Ala	Glu	Gln	Ser	Arg	Ala	Ala	Ile	Asn	Lys	Trp	Val	Ser	Asn	
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30	Lys	Thr	Glu	Gly	Arg	Ile	Thr	Asp	Val	Ile	Pro	Ser	Glu	Ala	Ile	Asn	
			195					200					205				
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		210					215					220					
40	Trp	Lys	Ser	Lys	Phe	Ser	Pro	Glu	Asn	Thr	Arg	Lys	Glu	Leu	Phe	Tyr	
	225					230					235					240	
45	Lys	Ala	Asp	Gly	Glu	Ser	Cys	Ser	Ala	Ser	Met	Met	Tyr	Gln	Glu	Gly	
					245					250					255		
50	Lys	Phe	Arg	Tyr	Arg	Arg	Val	Ala	Glu	Gly	Thr	Gln	Val	Leu	Glu	Leu	
				260					265					270			
55	Pro	Phe	Lys	Gly	Asp	Asp	Ile	Thr	Met	Val	Leu	Ile	Leu	Pro	Lys	Pro	
			275					280					285				
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		290					295					300					
65	Gln	Glu	Trp	Leu	Asp	Glu	Leu	Glu	Glu	Met	Met	Leu	Val	Val	His	Met	
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Asp Met Gly Leu Val Asp Leu Phe Ser Pro Glu Lys Ser Lys Leu Pro
340 345 350

5 Gly Ile Val Ala Glu Gly Arg Asp Asp Leu Tyr Val Ser Asp Ala Phe
355 360 365

10 His Lys Ala Phe Leu Glu Val Asn Glu Glu Gly Ser Glu Ala Ala Ala
370 375 380

15 Ser Thr Ala Val Val Ile Ala Gly Ser Leu Asn Pro Asn Arg Val Thr
385 390 395 400

20 Phe Lys Ala Asn Arg Pro Phe Leu Val Phe Ile Arg Glu Val Pro Leu
405 410 415

25 Asn Thr Ile Ile Phe Met Gly Arg Val Ala Asn Pro Cys Val Lys
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EP 2 379 101 B1

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5	atg	aat	ccc	atg	tgc	att	tac	cgc	tcc	ccg	gag	aag	aag	gca	act	gag	96
	Met	Asn	Pro	Met	Cys	Ile	Tyr	Arg	Ser	Pro	Glu	Lys	Lys	Ala	Thr	Glu	
				20					25					30			
10	gat	gag	ggc	tca	gaa	cag	aag	atc	ccg	gag	gcc	acc	aac	cgg	cgt	gtc	144
	Asp	Glu	Gly	Ser	Glu	Gln	Lys	Ile	Pro	Glu	Ala	Thr	Asn	Arg	Arg	Val	
				35				40					45				
15	tgg	gaa	ctg	tcc	aag	gcc	aat	tcc	cgc	ttt	gct	acc	act	ttc	tat	cag	192
	Trp	Glu	Leu	Ser	Lys	Ala	Asn	Ser	Arg	Phe	Ala	Thr	Thr	Phe	Tyr	Gln	
		50					55					60					
20	cac	ctg	gca	gat	tcc	aag	aat	gac	aat	gat	aac	att	ttc	ctg	tca	ccc	240
	His	Leu	Ala	Asp	Ser	Lys	Asn	Asp	Asn	Asp	Asn	Ile	Phe	Leu	Ser	Pro	
	65					70					75					80	
25	ctg	agt	atc	tcc	acg	gct	ttt	gct	atg	acc	aag	ctg	ggg	gcc	tgt	aat	288
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		Glu	Lys	Thr	Ser	Asp	Gln	Ile	His	Phe	Phe	Phe	Ala	Lys	Leu	Asn	Cys	
					115				120					125				
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10		Arg	Leu	Tyr	Arg	Lys	Ala	Asn	Lys	Ser	Ser	Lys	Leu	Val	Ser	Ala	Asn	
			130					135					140					
		cgc	ctt	ttt	gga	gac	aaa	tcc	ctt	acc	ttc	aat	gag	acc	tac	cag	gac	480
15		Arg	Leu	Phe	Gly	Asp	Lys	Ser	Leu	Thr	Phe	Asn	Glu	Thr	Tyr	Gln	Asp	
		145					150					155					160	
		atc	agt	gag	ttg	gta	tat	gga	gcc	aag	ctc	cag	ccc	ctg	gac	ttc	aag	528
		Ile	Ser	Glu	Leu	Val	Tyr	Gly	Ala	Lys	Leu	Gln	Pro	Leu	Asp	Phe	Lys	
						165					170					175		
20		gaa	aat	gca	gag	caa	tcc	aga	gcg	gcc	atc	aac	aaa	tgg	gtg	tcc	aat	576
		Glu	Asn	Ala	Glu	Gln	Ser	Arg	Ala	Ala	Ile	Asn	Lys	Trp	Val	Ser	Asn	
					180					185					190			
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25		Lys	Thr	Glu	Gly	Arg	Ile	Thr	Asp	Val	Ile	Pro	Ser	Glu	Ala	Ile	Asn	
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30		Glu	Leu	Thr	Val	Leu	Val	Leu	Val	Asn	Thr	Ile	Tyr	Phe	Lys	Gly	Leu	
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40		Lys	Phe	Arg	Tyr	Arg	Arg	Val	Ala	Glu	Gly	Thr	Gln	Val	Leu	Glu	Leu	
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45		Pro	Phe	Lys	Gly	Asp	Asp	Ile	Thr	Met	Val	Leu	Ile	Leu	Pro	Lys	Pro	
				275					280					285				
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		Glu	Lys	Ser	Leu	Ala	Lys	Val	Glu	Lys	Glu	Leu	Thr	Pro	Glu	Val	Leu	
			290					295					300					
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		Gln	Glu	Trp	Leu	Asp	Glu	Leu	Glu	Glu	Met	Met	Leu	Val	Val	His	Met	
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	Asp Met Gly Leu Val Asp Leu Phe Ser Pro Glu Lys Ser Lys Leu Pro	
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5	ggt att gtt gca gaa ggc cga gat gac ctc tat gtc tca gat gca ttc	1104
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10	cat aag gca ttt ctt gag gta aat gaa gaa ggc agt gaa gca gct gca	1152
	His Lys Ala Phe Leu Glu Val Asn Glu Glu Gly Ser Glu Ala Ala Ala	
	370 375 380	
15	agt acc gct gtt gtg att gct ggc cgt cta aac ccc aac agg gtg act	1200
	Ser Thr Ala Val Val Ile Ala Gly Arg Leu Asn Pro Asn Arg Val Thr	
	385 390 395 400	
20	ttc aag gcc aac agg cct ttc ctg gtt ttt ata aga gaa gtt cct ctg	1248
	Phe Lys Ala Asn Arg Pro Phe Leu Val Phe Ile Arg Glu Val Pro Leu	
	405 410 415	
25	aac act att atc ttc atg ggc aga gta gcc aac cct tgt gtt aag	1293
	Asn Thr Ile Ile Phe Met Gly Arg Val Ala Asn Pro Cys Val Lys	
	420 425 430	
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5 Met Asn Pro Met Cys Ile Tyr Arg Ser Pro Glu Lys Lys Ala Thr Glu
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10 Asp Glu Gly Ser Glu Gln Lys Ile Pro Glu Ala Thr Asn Arg Arg Val
35 40 45

15 Trp Glu Leu Ser Lys Ala Asn Ser Arg Phe Ala Thr Thr Phe Tyr Gln
50 55 60

20 His Leu Ala Asp Ser Lys Asn Asp Asn Asp Asn Ile Phe Leu Ser Pro
65 70 75 80

25 Leu Ser Ile Ser Thr Ala Phe Ala Met Thr Lys Leu Gly Ala Cys Asn
85 90 95

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			115					120					125			
10	Arg	Leu	Tyr	Arg	Lys	Ala	Asn	Lys	Ser	Ser	Lys	Leu	Val	Ser	Ala	Asn
		130					135					140				
15	Arg	Leu	Phe	Gly	Asp	Lys	Ser	Leu	Thr	Phe	Asn	Glu	Thr	Tyr	Gln	Asp
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20	Ile	Ser	Glu	Leu	Val	Tyr	Gly	Ala	Lys	Leu	Gln	Pro	Leu	Asp	Phe	Lys
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25	Glu	Asn	Ala	Glu	Gln	Ser	Arg	Ala	Ala	Ile	Asn	Lys	Trp	Val	Ser	Asn
				180					185					190		
30	Lys	Thr	Glu	Gly	Arg	Ile	Thr	Asp	Val	Ile	Pro	Ser	Glu	Ala	Ile	Asn
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35	Glu	Leu	Thr	Val	Leu	Val	Leu	Val	Asn	Thr	Ile	Tyr	Phe	Lys	Gly	Leu
		210					215					220				
40	Trp	Lys	Ser	Lys	Phe	Ser	Pro	Glu	Asn	Thr	Arg	Lys	Glu	Leu	Phe	Tyr
	225					230					235					240
45	Lys	Ala	Asp	Gly	Glu	Ser	Cys	Ser	Ala	Ser	Met	Met	Tyr	Gln	Glu	Gly
					245					250					255	
50	Lys	Phe	Arg	Tyr	Arg	Arg	Val	Ala	Glu	Gly	Thr	Gln	Val	Leu	Glu	Leu
				260					265					270		
55	Pro	Phe	Lys	Gly	Asp	Asp	Ile	Thr	Met	Val	Leu	Ile	Leu	Pro	Lys	Pro
			275					280					285			
60	Glu	Lys	Ser	Leu	Ala	Lys	Val	Glu	Lys	Glu	Leu	Thr	Pro	Glu	Val	Leu
		290					295					300				
65	Gln	Glu	Trp	Leu	Asp	Glu	Leu	Glu	Glu	Met	Met	Leu	Val	Val	His	Met
	305					310					315					320
70	Pro	Arg	Phe	Arg	Ile	Glu	Asp	Gly	Phe	Ser	Leu	Lys	Glu	Gln	Leu	Gln
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Asp Met Gly Leu Val Asp Leu Phe Ser Pro Glu Lys Ser Lys Leu Pro
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5 Gly Ile Val Ala Glu Gly Arg Asp Asp Leu Tyr Val Ser Asp Ala Phe
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10 His Lys Ala Phe Leu Glu Val Asn Glu Glu Gly Ser Glu Ala Ala Ala
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15 Ser Thr Ala Val Val Ile Ala Gly Arg Leu Asn Pro Asn Arg Val Thr
385 390 395 400

20 Phe Lys Ala Asn Arg Pro Phe Leu Val Phe Ile Arg Glu Val Pro Leu
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	Met	Asn	Pro	Met	Cys	Ile	Tyr	Arg	Ser	Pro	Glu	Lys	Lys	Ala	Thr	Glu	
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10	gat	gag	ggc	tca	gaa	cag	aag	atc	ccg	gag	gcc	acc	aac	cgg	cgt	gtc	144
	Asp	Glu	Gly	Ser	Glu	Gln	Lys	Ile	Pro	Glu	Ala	Thr	Asn	Arg	Arg	Val	
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15	tgg	gaa	ctg	tcc	aag	gcc	aat	tcc	cgc	ttt	gct	acc	act	ttc	tat	cag	192
	Trp	Glu	Leu	Ser	Lys	Ala	Asn	Ser	Arg	Phe	Ala	Thr	Thr	Phe	Tyr	Gln	
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20	cac	ctg	gca	gat	tcc	aag	aat	gac	aat	gat	aac	att	ttc	ctg	tca	ccc	240
	His	Leu	Ala	Asp	Ser	Lys	Asn	Asp	Asn	Asp	Asn	Ile	Phe	Leu	Ser	Pro	
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	Leu	Ser	Ile	Ser	Thr	Ala	Phe	Ala	Met	Thr	Lys	Leu	Gly	Ala	Cys	Asn	
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	Glu	Lys	Thr	Ser	Asp	Gln	Ile	His	Phe	Phe	Phe	Ala	Lys	Leu	Asn	Cys	
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	Arg	Leu	Phe	Gly	Asp	Lys	Ser	Leu	Thr	Phe	Asn	Glu	Thr	Tyr	Gln	Asp	
	145				150						155				160		
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	Ile	Ser	Glu	Leu	Val	Tyr	Gly	Ala	Lys	Leu	Gln	Pro	Leu	Asp	Phe	Lys	
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25	gaa	aat	gca	gag	caa	tcc	aga	gcg	gcc	atc	aac	aaa	tgg	gtg	tcc	aat	576
	Glu	Asn	Ala	Glu	Gln	Ser	Arg	Ala	Ala	Ile	Asn	Lys	Trp	Val	Ser	Asn	
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	Glu	Leu	Thr	Val	Leu	Val	Leu	Val	Asn	Thr	Ile	Tyr	Phe	Lys	Gly	Leu	
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	Trp	Lys	Ser	Lys	Phe	Ser	Pro	Glu	Asn	Thr	Arg	Lys	Glu	Leu	Phe	Tyr	
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	Lys	Ala	Asp	Gly	Glu	Ser	Cys	Ser	Ala	Ser	Met	Met	Tyr	Gln	Glu	Gly	
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	Pro	Phe	Lys	Gly	Asp	Asp	Ile	Thr	Met	Val	Leu	Ile	Leu	Pro	Lys	Pro	
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	Gln	Glu	Trp	Leu	Asp	Glu	Leu	Glu	Glu	Met	Met	Leu	Val	Val	His	Met	
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	Gly	Ile	Val	Ala	Glu	Gly	Arg	Asp	Asp	Leu	Tyr	Val	Ser	Asp	Ala	Phe	
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	Ser	Thr	Ala	Val	Val	Ile	Ala	Gly	Arg	Ser	Leu	Asn	Pro	Asn	Arg	Val	
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15	act	ttc	aag	gcc	aac	agg	cct	ttc	ctg	gtt	ttt	ata	aga	gaa	gtt	cct	1248
	Thr	Phe	Lys	Ala	Asn	Arg	Pro	Phe	Leu	Val	Phe	Ile	Arg	Glu	Val	Pro	
				405						410					415		
20	ctg	aac	act	att	atc	ttc	atg	ggc	aga	gta	gcc	aac	cct	tgt	gtt	aag	1296
	Leu	Asn	Thr	Ile	Ile	Phe	Met	Gly	Arg	Val	Ala	Asn	Pro	Cys	Val	Lys	
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5 Met Asn Pro Met Cys Ile Tyr Arg Ser Pro Glu Lys Lys Ala Thr Glu
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10 Asp Glu Gly Ser Glu Gln Lys Ile Pro Glu Ala Thr Asn Arg Arg Val
35 40 45

15 Trp Glu Leu Ser Lys Ala Asn Ser Arg Phe Ala Thr Thr Phe Tyr Gln
50 55 60

20 His Leu Ala Asp Ser Lys Asn Asp Asn Asp Asn Ile Phe Leu Ser Pro
65 70 75 80

25 Leu Ser Ile Ser Thr Ala Phe Ala Met Thr Lys Leu Gly Ala Cys Asn
85 90 95

Asp Thr Leu Gln Gln Leu Met Glu Val Phe Lys Phe Asp Thr Ile Ser

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	Gln	Glu	Trp	Leu	Asp	Glu	Leu	Glu	Glu	Met	Met	Leu	Val	Val	His	Met	
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5 Gly Ile Val Ala Glu Gly Arg Asp Asp Leu Tyr Val Ser Asp Ala Phe
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10 His Lys Ala Phe Leu Glu Val Asn Glu Glu Gly Ser Glu Ala Ala Ala
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	Met	Asn	Pro	Met	Cys	Ile	Tyr	Arg	Ser	Pro	Glu	Lys	Lys	Ala	Thr	Glu	
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	Trp	Glu	Leu	Ser	Lys	Ala	Asn	Ser	Arg	Phe	Ala	Thr	Thr	Phe	Tyr	Gln	
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25	ctg	agt	atc	tcc	acg	gct	ttt	gct	atg	acc	aag	ctg	ggg	gcc	tgt	aat	288
	Leu	Ser	Ile	Ser	Thr	Ala	Phe	Ala	Met	Thr	Lys	Leu	Gly	Ala	Cys	Asn	
					85				90					95			
30	gac	acc	ctc	cag	caa	ctg	atg	gag	gta	ttt	aag	ttt	gac	acc	ata	tct	336
	Asp	Thr	Leu	Gln	Gln	Leu	Met	Glu	Val	Phe	Lys	Phe	Asp	Thr	Ile	Ser	

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10	cga ctc tat cga aaa gcc cag aaa tcc tcc aag tta gta tca gcc aat Arg Leu Tyr Arg Lys Ala Gln Lys Ser Ser Lys Leu Val Ser Ala Asn 130 135 140			432
15	cgc ctt ttt gga gac aaa tcc ctt acc ttc aat gag acc tac cag gac Arg Leu Phe Gly Asp Lys Ser Leu Thr Phe Asn Glu Thr Tyr Gln Asp 145 150 155 160			480
20	atc agt gag ttg gta tat gga gcc aag ctc cag ccc ctg gac ttc aag Ile Ser Glu Leu Val Tyr Gly Ala Lys Leu Gln Pro Leu Asp Phe Lys 165 170 175			528
25	gaa aat gca gag caa tcc aga gcg gcc atc aac aaa tgg gtg tcc aat Glu Asn Ala Glu Gln Ser Arg Ala Ala Ile Asn Lys Trp Val Ser Asn 180 185 190			576
30	aag acc gaa ggc cga atc acc gat gtc att ccc tcg gaa gcc atc aat Lys Thr Glu Gly Arg Ile Thr Asp Val Ile Pro Ser Glu Ala Ile Asn 195 200 205			624
35	gag ctc act gtt ctg gtg ctg gtt aac acc att tac ttc aag ggc ctg Glu Leu Thr Val Leu Val Leu Val Asn Thr Ile Tyr Phe Lys Gly Leu 210 215 220			672
40	tgg aag tca aag ttc agc cct gag aac aca agg aag gaa ctg ttc tac Trp Lys Ser Lys Phe Ser Pro Glu Asn Thr Arg Lys Glu Leu Phe Tyr 225 230 235 240			720
45	aag gct gat gga gag tcg tgt tca gca tct atg atg tac cag gaa ggc Lys Ala Asp Gly Glu Ser Cys Ser Ala Ser Met Met Tyr Gln Glu Gly 245 250 255			768
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65	caa gag tgg ctg gat gaa ttg gag gag atg atg ctg gtg gtc cac atg Gln Glu Trp Leu Asp Glu Leu Glu Glu Met Met Leu Val Val His Met 305 310 315 320			960
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75	gac atg ggc ctt gtc gat ctg ttc agc cct gaa aag tcc aaa ctc cca Asp Met Gly Leu Val Asp Leu Phe Ser Pro Glu Lys Ser Lys Leu Pro 340 345 350 355			1056

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15	agt acc gct gtt gtg att gct ggc cat tcg cta aac ccc aac agg gtg Ser Thr Ala Val Val Ile Ala Gly His Ser Leu Asn Pro Asn Arg Val 385 390 395 400			1200
20	act ttc aag gcc aac agg cct ttc ctg gtt ttt ata aga gaa gtt cct Thr Phe Lys Ala Asn Arg Pro Phe Leu Val Phe Ile Arg Glu Val Pro 405 410 415			1248
25	ctg aac act att atc ttc atg ggc aga gta gcc aac cct tgt gtt aag Leu Asn Thr Ile Ile Phe Met Gly Arg Val Ala Asn Pro Cys Val Lys 420 425 430			1296
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5	Met	Asn	Pro	Met	Cys	Ile	Tyr	Arg	Ser	Pro	Glu	Lys	Lys	Ala	Thr	Glu
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10	Asp	Glu	Gly	Ser	Glu	Gln	Lys	Ile	Pro	Glu	Ala	Thr	Asn	Arg	Arg	Val
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15	Trp	Glu	Leu	Ser	Lys	Ala	Asn	Ser	Arg	Phe	Ala	Thr	Thr	Phe	Tyr	Gln
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20	His	Leu	Ala	Asp	Ser	Lys	Asn	Asp	Asn	Asp	Asn	Ile	Phe	Leu	Ser	Pro
	65					70					75				80	
25	Leu	Ser	Ile	Ser	Thr	Ala	Phe	Ala	Met	Thr	Lys	Leu	Gly	Ala	Cys	Asn
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35																
40																
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5	Arg	Leu	Tyr	Arg	Lys	Ala	Gln	Lys	Ser	Ser	Lys	Leu	Val	Ser	Ala	Asn	
10	Arg	Leu	Phe	Gly	Asp	Lys	Ser	Leu	Thr	Phe	Asn	Glu	Thr	Tyr	Gln	Asp	
15	Ile	Ser	Glu	Leu	Val	Tyr	Gly	Ala	Lys	Leu	Gln	Pro	Leu	Asp	Phe	Lys	
20	Glu	Asn	Ala	Glu	Gln	Ser	Arg	Ala	Ala	Ile	Asn	Lys	Trp	Val	Ser	Asn	
25	Lys	Thr	Glu	Gly	Arg	Ile	Thr	Asp	Val	Ile	Pro	Ser	Glu	Ala	Ile	Asn	
30	Glu	Leu	Thr	Val	Leu	Val	Leu	Val	Asn	Thr	Ile	Tyr	Phe	Lys	Gly	Leu	
35	Trp	Lys	Ser	Lys	Phe	Ser	Pro	Glu	Asn	Thr	Arg	Lys	Glu	Leu	Phe	Tyr	
40	Lys	Ala	Asp	Gly	Glu	Ser	Cys	Ser	Ala	Ser	Met	Met	Tyr	Gln	Glu	Gly	
45	Lys	Phe	Arg	Tyr	Arg	Arg	Val	Ala	Glu	Gly	Thr	Gln	Val	Leu	Glu	Leu	
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65	Pro	Arg	Phe	Arg	Ile	Glu	Asp	Gly	Phe	Ser	Leu	Lys	Glu	Gln	Leu	Gln	
70	Asp	Met	Gly	Leu	Val	Asp	Leu	Phe	Ser	Pro	Glu	Lys	Ser	Lys	Leu	Pro	

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Gly Ile Val Ala Glu Gly Arg Asp Asp Leu Tyr Val Ser Asp Ala Phe
355 360 365

5 His Lys Ala Phe Leu Glu Val Asn Glu Glu Gly Ser Glu Ala Ala Ala
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10 Ser Thr Ala Val Val Ile Ala Gly His Ser Leu Asn Pro Asn Arg Val
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15 Thr Phe Lys Ala Asn Arg Pro Phe Leu Val Phe Ile Arg Glu Val Pro
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Met Asn Pro Met Cys Ile Tyr Arg Ser Pro Glu Lys Lys Ala Thr Glu
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Asp Glu Gly Ser Glu Gln Lys Ile Pro Glu Ala Thr Asn Arg Arg Val
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tgg gaa ctg tcc aag gcc aat tcc cgc ttt gct acc act ttc tat cag 192
Trp Glu Leu Ser Lys Ala Asn Ser Arg Phe Ala Thr Thr Phe Tyr Gln
50 55 60

cac ctg gca gat tcc aag aat gac aat gat aac att ttc ctg tca ccc 240
His Leu Ala Asp Ser Lys Asn Asp Asn Asp Asn Ile Phe Leu Ser Pro
50 65 70 75 80

ctg agt atc tcc acg gct ttt gct atg acc aag ctg ggt gcc tgt aat 288
Leu Ser Ile Ser Thr Ala Phe Ala Met Thr Lys Leu Gly Ala Cys Asn
85 90 95

gac acc ctc cag caa ctg atg gag gta ttt aag ttt gac acc ata tct 336
Asp Thr Leu Gln Gln Leu Met Glu Val Phe Lys Phe Asp Thr Ile Ser
100 105 110

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		gag	aaa	aca	tct	gat	cag	atc	cac	ttc	ttc	ttt	gcc	aaa	ctg	aac	tgc	384
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		Glu	Asn	Ala	Glu	Gln	Ser	Arg	Ala	Ala	Ile	Asn	Lys	Trp	Val	Ser	Asn	
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		Lys	Phe	Arg	Tyr	Arg	Arg	Val	Ala	Glu	Gly	Thr	Gln	Val	Leu	Glu	Leu	
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		Pro	Arg	Phe	Arg	Ile	Glu	Asp	Gly	Phe	Ser	Leu	Lys	Glu	Gln	Leu	Gln	
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	ggt att gtt gca gaa ggc cga gat gac ctc tat gtc tca gat gca ttc	1104
	Gly Ile Val Ala Glu Gly Arg Asp Asp Leu Tyr Val Ser Asp Ala Phe	
	355 360 365	
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	His Lys Ala Phe Leu Glu Val Asn Glu Glu Gly Ser Glu Ala Ala Ala	
	370 375 380	
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	Ser Thr Ala Val Val Ile Ala Gly Arg Pro Ser Leu Asn Pro Asn Arg	
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15	gtg act ttc aag gcc aac agg cct ttc ctg gtt ttt ata aga gaa gtt	1248
	Val Thr Phe Lys Ala Asn Arg Pro Phe Leu Val Phe Ile Arg Glu Val	
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	cct ctg aac act att atc ttc atg ggc aga gta gcc aac cct tgt gtt	1296
	Pro Leu Asn Thr Ile Ile Phe Met Gly Arg Val Ala Asn Pro Cys Val	
	420 425 430	
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5 Met Asn Pro Met Cys Ile Tyr Arg Ser Pro Glu Lys Lys Ala Thr Glu
20 25 30

10 Asp Glu Gly Ser Glu Gln Lys Ile Pro Glu Ala Thr Asn Arg Arg Val
35 40 45

15 Trp Glu Leu Ser Lys Ala Asn Ser Arg Phe Ala Thr Thr Phe Tyr Gln
50 55 60

20 His Leu Ala Asp Ser Lys Asn Asp Asn Asp Asn Ile Phe Leu Ser Pro
65 70 75 80

25 Leu Ser Ile Ser Thr Ala Phe Ala Met Thr Lys Leu Gly Ala Cys Asn
85 90 95

Asp Thr Leu Gln Gln Leu Met Glu Val Phe Lys Phe Asp Thr Ile Ser

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20	Ile Ser Glu Leu Val Tyr Gly Ala Lys Leu Gln Pro Leu Asp Phe Lys 165 170 175		
25	Glu Asn Ala Glu Gln Ser Arg Ala Ala Ile Asn Lys Trp Val Ser Asn 180 185 190		
30	Lys Thr Glu Gly Arg Ile Thr Asp Val Ile Pro Ser Glu Ala Ile Asn 195 200 205		
35	Glu Leu Thr Val Leu Val Leu Val Asn Thr Ile Tyr Phe Lys Gly Leu 210 215 220		
40	Trp Lys Ser Lys Phe Ser Pro Glu Asn Thr Arg Lys Glu Leu Phe Tyr 225 230 235 240		
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5 Gly Ile Val Ala Glu Gly Arg Asp Asp Leu Tyr Val Ser Asp Ala Phe
355 360 365

10 His Lys Ala Phe Leu Glu Val Asn Glu Glu Gly Ser Glu Ala Ala Ala
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15 Ser Thr Ala Val Val Ile Ala Gly Arg Pro Ser Leu Asn Pro Asn Arg
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20 Val Thr Phe Lys Ala Asn Arg Pro Phe Leu Val Phe Ile Arg Glu Val
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5	atg aat ccc atg tgc att tac cgc tcc ccg gag aag aag gca act gag	96
	Met Asn Pro Met Cys Ile Tyr Arg Ser Pro Glu Lys Lys Ala Thr Glu	
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10	gat gag ggc tca gaa cag aag atc ccg gag gcc acc aac cgg cgt gtc	144
	Asp Glu Gly Ser Glu Gln Lys Ile Pro Glu Ala Thr Asn Arg Arg Val	
	35 40 45	
15	tgg gaa ctg tcc aag gcc aat tcc cgc ttt gct acc act ttc tat cag	192
	Trp Glu Leu Ser Lys Ala Asn Ser Arg Phe Ala Thr Thr Phe Tyr Gln	
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20	cac ctg gca gat tcc aag aat gac aat gat aac att ttc ctg tca ccc	240
	His Leu Ala Asp Ser Lys Asn Asp Asn Asp Asn Ile Phe Leu Ser Pro	
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25	ctg agt atc tcc acg gct ttt gct atg acc aag ctg ggt gcc tgt aat	288
	Leu Ser Ile Ser Thr Ala Phe Ala Met Thr Lys Leu Gly Ala Cys Asn	
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5	gac	acc	ctc	cag	caa	ctg	atg	gag	gta	ttt	aag	ttt	gac	acc	ata	tct						336
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	gag	aaa	aca	tct	gat	cag	atc	cac	ttc	ttc	ttt	gcc	aaa	ctg	aac	tgc						384
	Glu	Lys	Thr	Ser	Asp	Gln	Ile	His	Phe	Phe	Phe	Ala	Lys	Leu	Asn	Cys						
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	Arg	Leu	Tyr	Arg	Lys	Ala	Asn	Lys	Ser	Ser	Lys	Leu	Val	Ser	Ala	Asn						
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15	cgc	ctt	ttt	gga	gac	aaa	tcc	ctt	acc	ttc	aat	gag	acc	tac	cag	gac						480
	Arg	Leu	Phe	Gly	Asp	Lys	Ser	Leu	Thr	Phe	Asn	Glu	Thr	Tyr	Gln	Asp						
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20	atc	agt	gag	ttg	gta	tat	gga	gcc	aag	ctc	cag	ccc	ctg	gac	ttc	aag						528
	Ile	Ser	Glu	Leu	Val	Tyr	Gly	Ala	Lys	Leu	Gln	Pro	Leu	Asp	Phe	Lys						
					165					170					175							
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	Glu	Asn	Ala	Glu	Gln	Ser	Arg	Ala	Ala	Ile	Asn	Lys	Trp	Val	Ser	Asn						
					180				185					190								
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	Lys	Thr	Glu	Gly	Arg	Ile	Thr	Asp	Val	Ile	Pro	Ser	Glu	Ala	Ile	Asn						
				195				200					205									
30	gag	ctc	act	gtt	ctg	gtg	ctg	gtt	aac	acc	att	tac	ttc	aag	ggc	ctg						672
	Glu	Leu	Thr	Val	Leu	Val	Leu	Val	Asn	Thr	Ile	Tyr	Phe	Lys	Gly	Leu						
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	Lys	Phe	Arg	Tyr	Arg	Arg	Val	Ala	Glu	Gly	Thr	Gln	Val	Leu	Glu	Leu						
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				290			295					300										
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	Gln	Glu	Trp	Leu	Asp	Glu	Leu	Glu	Glu	Met	Met	Leu	Val	Val	His	Met						
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55	ccc	cgc	ttc	cgc	att	gag	gac	ggc	ttc	agt	ttg	aag	gag	cag	ctg	caa						1008
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10	ggt att gtt gca gaa ggc cga gat gac ctc tat gtc tca gat gca ttc Gly Ile Val Ala Glu Gly Arg Asp Asp Leu Tyr Val Ser Asp Ala Phe 355 360 365			1104
15	cat aag gca ttt ctt gag gta aat gaa gaa ggc agt gaa gca gct gca His Lys Ala Phe Leu Glu Val Asn Glu Glu Gly Ser Glu Ala Ala Ala 370 375 380			1152
20	agt acc gct gtt gtg att gct ggc cta aac ccc aac agg gtg act ttc Ser Thr Ala Val Val Ile Ala Gly Leu Asn Pro Asn Arg Val Thr Phe 385 390 395 400			1200
25	aag gcc aac agg cct ttc ctg gtt ttt ata aga gaa gtt cct ctg aac Lys Ala Asn Arg Pro Phe Leu Val Phe Ile Arg Glu Val Pro Leu Asn 405 410 415			1248
30	act att atc ttc atg ggc aga gta gcc aac cct tgt gtt aag Thr Ile Ile Phe Met Gly Arg Val Ala Asn Pro Cys Val Lys 420 425 430			1290
35	taaaatgttc ttattctttg cacctcttcc tatttttggg ttgtgaacag aagtaaaaat			1350
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5 Met Asn Pro Met Cys Ile Tyr Arg Ser Pro Glu Lys Lys Ala Thr Glu
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10 Asp Glu Gly Ser Glu Gln Lys Ile Pro Glu Ala Thr Asn Arg Arg Val
35 40 45

15 Trp Glu Leu Ser Lys Ala Asn Ser Arg Phe Ala Thr Thr Phe Tyr Gln
50 55 60

20 His Leu Ala Asp Ser Lys Asn Asp Asn Asp Asn Ile Phe Leu Ser Pro
65 70 75 80

25 Leu Ser Ile Ser Thr Ala Phe Ala Met Thr Lys Leu Gly Ala Cys Asn
85 90 95

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10	Arg	Leu	Tyr	Arg	Lys	Ala	Asn	Lys	Ser	Ser	Lys	Leu	Val	Ser	Ala	Asn	
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25	Glu	Asn	Ala	Glu	Gln	Ser	Arg	Ala	Ala	Ile	Asn	Lys	Trp	Val	Ser	Asn	
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65	Gln	Glu	Trp	Leu	Asp	Glu	Leu	Glu	Glu	Met	Met	Leu	Val	Val	His	Met	
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Asp Met Gly Leu Val Asp Leu Phe Ser Pro Glu Lys Ser Lys Leu Pro
340 345 350

5 Gly Ile Val Ala Glu Gly Arg Asp Asp Leu Tyr Val Ser Asp Ala Phe
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10 His Lys Ala Phe Leu Glu Val Asn Glu Glu Gly Ser Glu Ala Ala Ala
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15 Ser Thr Ala Val Val Ile Ala Gly Leu Asn Pro Asn Arg Val Thr Phe
385 390 395 400

20 Lys Ala Asn Arg Pro Phe Leu Val Phe Ile Arg Glu Val Pro Leu Asn
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	Met	Asn	Pro	Met	Cys	Ile	Tyr	Arg	Ser	Pro	Glu	Lys	Lys	Ala	Thr	Glu	
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10	gat	gag	ggc	tca	gaa	cag	aag	atc	ccg	gag	gcc	acc	aac	cgg	cgt	gtc	144
	Asp	Glu	Gly	Ser	Glu	Gln	Lys	Ile	Pro	Glu	Ala	Thr	Asn	Arg	Arg	Val	
			35					40					45				
15	tgg	gaa	ctg	tcc	aag	gcc	aat	tcc	cgc	ttt	gct	acc	act	ttc	tat	cag	192
	Trp	Glu	Leu	Ser	Lys	Ala	Asn	Ser	Arg	Phe	Ala	Thr	Thr	Phe	Tyr	Gln	
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	His	Leu	Ala	Asp	Ser	Lys	Asn	Asp	Asn	Asp	Asn	Ile	Phe	Leu	Ser	Pro	
	65					70					75					80	
25	ctg	agt	atc	tcc	acg	gct	ttt	gct	atg	acc	aag	ctg	ggg	gcc	tgt	aat	288
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		Glu	Lys	Thr	Ser	Asp	Gln	Ile	His	Phe	Phe	Phe	Ala	Lys	Leu	Asn	Cys	
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10		Arg	Leu	Tyr	Arg	Lys	Ala	Gln	Lys	Ser	Ser	Lys	Leu	Val	Ser	Ala	Asn	
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15		Arg	Leu	Phe	Gly	Asp	Lys	Ser	Leu	Thr	Phe	Asn	Glu	Thr	Tyr	Gln	Asp	
		145					150					155					160	
		atc	agt	gag	ttg	gta	tat	gga	gcc	aag	ctc	cag	ccc	ctg	gac	ttc	aag	528
		Ile	Ser	Glu	Leu	Val	Tyr	Gly	Ala	Lys	Leu	Gln	Pro	Leu	Asp	Phe	Lys	
						165					170					175		
20		gaa	aat	gca	gag	caa	tcc	aga	gcg	gcc	atc	aac	aaa	tgg	gtg	tcc	aat	576
		Glu	Asn	Ala	Glu	Gln	Ser	Arg	Ala	Ala	Ile	Asn	Lys	Trp	Val	Ser	Asn	
					180					185					190			
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25		Lys	Thr	Glu	Gly	Arg	Ile	Thr	Asp	Val	Ile	Pro	Ser	Glu	Ala	Ile	Asn	
				195					200					205				
		gag	ctc	act	gtt	ctg	gtg	ctg	gtt	aac	acc	att	tac	ttc	aag	ggc	ctg	672
30		Glu	Leu	Thr	Val	Leu	Val	Leu	Val	Asn	Thr	Ile	Tyr	Phe	Lys	Gly	Leu	
			210					215					220					
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		Trp	Lys	Ser	Lys	Phe	Ser	Pro	Glu	Asn	Thr	Arg	Lys	Glu	Leu	Phe	Tyr	
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35		aag	gct	gat	gga	gag	tcg	tgt	tca	gca	tct	atg	atg	tac	cag	gaa	ggc	768
		Lys	Ala	Asp	Gly	Glu	Ser	Cys	Ser	Ala	Ser	Met	Met	Tyr	Gln	Glu	Gly	
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40		Lys	Phe	Arg	Tyr	Arg	Arg	Val	Ala	Glu	Gly	Thr	Gln	Val	Leu	Glu	Leu	
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		ccc	ttc	aaa	ggg	gat	gac	atc	acc	atg	gtc	ctc	atc	ttg	ccc	aag	cct	864
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				275					280					285				
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		Glu	Lys	Ser	Leu	Ala	Lys	Val	Glu	Lys	Glu	Leu	Thr	Pro	Glu	Val	Leu	
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55		Pro	Arg	Phe	Arg	Ile	Glu	Asp	Gly	Phe	Ser	Leu	Lys	Glu	Gln	Leu	Gln	
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	gac atg ggc ctt gtc gat ctg ttc agc cct gaa aag tcc aaa ctc cca	1056
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5	ggt att gtt gca gaa ggc cga gat gac ctc tat gtc tca gat gca ttc	1104
	Gly Ile Val Ala Glu Gly Arg Asp Asp Leu Tyr Val Ser Asp Ala Phe	
	355 360 365	
10	cat aag gca ttt ctt gag gta aat gaa gaa ggc agt gaa gca gct gca	1152
	His Lys Ala Phe Leu Glu Val Asn Glu Glu Gly Ser Glu Ala Ala Ala	
	370 375 380	
15	agt acc gct gtt gtg att gct ggc tcg cta aac ccc aac agg gtg act	1200
	Ser Thr Ala Val Val Ile Ala Gly Ser Leu Asn Pro Asn Arg Val Thr	
	385 390 395 400	
20	ttc aag gcc aac agg cct ttc ctg gtt ttt ata aga gaa gtt cct ctg	1248
	Phe Lys Ala Asn Arg Pro Phe Leu Val Phe Ile Arg Glu Val Pro Leu	
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25	aac act att atc ttc atg ggc aga gta gcc aac cct tgt gtt aag	1293
	Asn Thr Ile Ile Phe Met Gly Arg Val Ala Asn Pro Cys Val Lys	
	420 425 430	
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5 Met Asn Pro Met Cys Ile Tyr Arg Ser Pro Glu Lys Lys Ala Thr Glu
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10 Asp Glu Gly Ser Glu Gln Lys Ile Pro Glu Ala Thr Asn Arg Arg Val
35 40 45

15 Trp Glu Leu Ser Lys Ala Asn Ser Arg Phe Ala Thr Thr Phe Tyr Gln
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20 His Leu Ala Asp Ser Lys Asn Asp Asn Asp Asn Ile Phe Leu Ser Pro
65 70 75 80

25 Leu Ser Ile Ser Thr Ala Phe Ala Met Thr Lys Leu Gly Ala Cys Asn
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			115					120					125			
10	Arg	Leu	Tyr	Arg	Lys	Ala	Gln	Lys	Ser	Ser	Lys	Leu	Val	Ser	Ala	Asn
		130					135					140				
15	Arg	Leu	Phe	Gly	Asp	Lys	Ser	Leu	Thr	Phe	Asn	Glu	Thr	Tyr	Gln	Asp
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20	Ile	Ser	Glu	Leu	Val	Tyr	Gly	Ala	Lys	Leu	Gln	Pro	Leu	Asp	Phe	Lys
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25	Glu	Asn	Ala	Glu	Gln	Ser	Arg	Ala	Ala	Ile	Asn	Lys	Trp	Val	Ser	Asn
				180					185					190		
30	Lys	Thr	Glu	Gly	Arg	Ile	Thr	Asp	Val	Ile	Pro	Ser	Glu	Ala	Ile	Asn
			195					200					205			
35	Glu	Leu	Thr	Val	Leu	Val	Leu	Val	Asn	Thr	Ile	Tyr	Phe	Lys	Gly	Leu
		210					215					220				
40	Trp	Lys	Ser	Lys	Phe	Ser	Pro	Glu	Asn	Thr	Arg	Lys	Glu	Leu	Phe	Tyr
	225					230					235					240
45	Lys	Ala	Asp	Gly	Glu	Ser	Cys	Ser	Ala	Ser	Met	Met	Tyr	Gln	Glu	Gly
					245					250					255	
50	Lys	Phe	Arg	Tyr	Arg	Arg	Val	Ala	Glu	Gly	Thr	Gln	Val	Leu	Glu	Leu
				260					265					270		
55	Pro	Phe	Lys	Gly	Asp	Asp	Ile	Thr	Met	Val	Leu	Ile	Leu	Pro	Lys	Pro
			275					280					285			
60	Glu	Lys	Ser	Leu	Ala	Lys	Val	Glu	Lys	Glu	Leu	Thr	Pro	Glu	Val	Leu
		290					295					300				
65	Gln	Glu	Trp	Leu	Asp	Glu	Leu	Glu	Glu	Met	Met	Leu	Val	Val	His	Met
	305					310					315					320
70	Pro	Arg	Phe	Arg	Ile	Glu	Asp	Gly	Phe	Ser	Leu	Lys	Glu	Gln	Leu	Gln
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Asp Met Gly Leu Val Asp Leu Phe Ser Pro Glu Lys Ser Lys Leu Pro
340 345 350

5 Gly Ile Val Ala Glu Gly Arg Asp Asp Leu Tyr Val Ser Asp Ala Phe
355 360 365

10 His Lys Ala Phe Leu Glu Val Asn Glu Glu Gly Ser Glu Ala Ala Ala
370 375 380

15 Ser Thr Ala Val Val Ile Ala Gly Ser Leu Asn Pro Asn Arg Val Thr
385 390 395 400

20 Phe Lys Ala Asn Arg Pro Phe Leu Val Phe Ile Arg Glu Val Pro Leu
405 410 415

25 Asn Thr Ile Ile Phe Met Gly Arg Val Ala Asn Pro Cys Val Lys
420 425 430

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	Met	Asn	Pro	Met	Cys	Ile	Tyr	Arg	Ser	Pro	Glu	Lys	Lys	Ala	Thr	Glu	
				20					25					30			
10	gat	gag	ggc	tca	gaa	cag	aag	atc	ccg	gag	gcc	acc	aac	cgg	cgt	gtc	144
	Asp	Glu	Gly	Ser	Glu	Gln	Lys	Ile	Pro	Glu	Ala	Thr	Asn	Arg	Arg	Val	
				35				40					45				
15	tgg	gaa	ctg	tcc	aag	gcc	aat	tcc	cgc	ttt	gct	acc	act	ttc	tat	cag	192
	Trp	Glu	Leu	Ser	Lys	Ala	Asn	Ser	Arg	Phe	Ala	Thr	Thr	Phe	Tyr	Gln	
		50					55					60					
20	cac	ctg	gca	gat	tcc	aag	aat	gac	aat	gat	aac	att	ttc	ctg	tca	ccc	240
	His	Leu	Ala	Asp	Ser	Lys	Asn	Asp	Asn	Asp	Asn	Ile	Phe	Leu	Ser	Pro	
	65					70					75					80	
25	ctg	agt	atc	tcc	acg	gct	ttt	gct	atg	acc	aag	ctg	ggg	gcc	tgt	aat	288
	Leu	Ser	Ile	Ser	Thr	Ala	Phe	Ala	Met	Thr	Lys	Leu	Gly	Ala	Cys	Asn	
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5		gag	aaa	aca	tct	gat	cag	atc	cac	ttc	ttc	ttt	gcc	aaa	ctg	aac	tgc	384
		Glu	Lys	Thr	Ser	Asp	Gln	Ile	His	Phe	Phe	Phe	Ala	Lys	Leu	Asn	Cys	
					115				120					125				
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10		Arg	Leu	Tyr	Arg	Lys	Ala	Gln	Lys	Ser	Ser	Lys	Leu	Val	Ser	Ala	Asn	
			130					135						140				
		cgc	ctt	ttt	gga	gac	aaa	tcc	ctt	acc	ttc	aat	gag	acc	tac	cag	gac	480
15		Arg	Leu	Phe	Gly	Asp	Lys	Ser	Leu	Thr	Phe	Asn	Glu	Thr	Tyr	Gln	Asp	
			145				150					155					160	
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		Ile	Ser	Glu	Leu	Val	Tyr	Gly	Ala	Lys	Leu	Gln	Pro	Leu	Asp	Phe	Lys	
						165						170				175		
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		Glu	Asn	Ala	Glu	Gln	Ser	Arg	Ala	Ala	Ile	Asn	Lys	Trp	Val	Ser	Asn	
					180					185					190			
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25		Lys	Thr	Glu	Gly	Arg	Ile	Thr	Asp	Val	Ile	Pro	Ser	Glu	Ala	Ile	Asn	
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			210					215					220					
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40		Lys	Phe	Arg	Tyr	Arg	Arg	Val	Ala	Glu	Gly	Thr	Gln	Val	Leu	Glu	Leu	
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45		Pro	Phe	Lys	Gly	Asp	Asp	Ile	Thr	Met	Val	Leu	Ile	Leu	Pro	Lys	Pro	
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		Glu	Lys	Ser	Leu	Ala	Lys	Val	Glu	Lys	Glu	Leu	Thr	Pro	Glu	Val	Leu	
			290					295					300					
50		caa	gag	tgg	ctg	gat	gaa	ttg	gag	gag	atg	atg	ctg	gtg	gtc	cac	atg	960
		Gln	Glu	Trp	Leu	Asp	Glu	Leu	Glu	Glu	Met	Met	Leu	Val	Val	His	Met	
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		ccc	cgc	ttc	cgc	att	gag	gac	ggc	ttc	agt	ttg	aag	gag	cag	ctg	caa	1008
55		Pro	Arg	Phe	Arg	Ile	Glu	Asp	Gly	Phe	Ser	Leu	Lys	Glu	Gln	Leu	Gln	
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	Asp Met Gly Leu Val Asp Leu Phe Ser Pro Glu Lys Ser Lys Leu Pro	
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5	ggt att gtt gca gaa ggc cga gat gac ctc tat gtc tca gat gca ttc	1104
	Gly Ile Val Ala Glu Gly Arg Asp Asp Leu Tyr Val Ser Asp Ala Phe	
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	His Lys Ala Phe Leu Glu Val Asn Glu Glu Gly Ser Glu Ala Ala Ala	
	370 375 380	
15	agt acc gct gtt gtg att gct ggc cgt cta aac ccc aac agg gtg act	1200
	Ser Thr Ala Val Val Ile Ala Gly Arg Leu Asn Pro Asn Arg Val Thr	
	385 390 395 400	
20	ttc aag gcc aac agg cct ttc ctg gtt ttt ata aga gaa gtt cct ctg	1248
	Phe Lys Ala Asn Arg Pro Phe Leu Val Phe Ile Arg Glu Val Pro Leu	
	405 410 415	
25	aac act att atc ttc atg ggc aga gta gcc aac cct tgt gtt aag	1293
	Asn Thr Ile Ile Phe Met Gly Arg Val Ala Asn Pro Cys Val Lys	
	420 425 430	
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5 Met Asn Pro Met Cys Ile Tyr Arg Ser Pro Glu Lys Lys Ala Thr Glu
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10 Asp Glu Gly Ser Glu Gln Lys Ile Pro Glu Ala Thr Asn Arg Arg Val
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15 Trp Glu Leu Ser Lys Ala Asn Ser Arg Phe Ala Thr Thr Phe Tyr Gln
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20 His Leu Ala Asp Ser Lys Asn Asp Asn Asp Asn Ile Phe Leu Ser Pro
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25 Leu Ser Ile Ser Thr Ala Phe Ala Met Thr Lys Leu Gly Ala Cys Asn
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25	Glu	Asn	Ala	Glu	Gln	Ser	Arg	Ala	Ala	Ile	Asn	Lys	Trp	Val	Ser	Asn	
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45	Lys	Ala	Asp	Gly	Glu	Ser	Cys	Ser	Ala	Ser	Met	Met	Tyr	Gln	Glu	Gly	
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		290					295					300					
65	Gln	Glu	Trp	Leu	Asp	Glu	Leu	Glu	Glu	Met	Met	Leu	Val	Val	His	Met	
	305					310					315					320	
70	Pro	Arg	Phe	Arg	Ile	Glu	Asp	Gly	Phe	Ser	Leu	Lys	Glu	Gln	Leu	Gln	
					325					330					335		

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Asp Met Gly Leu Val Asp Leu Phe Ser Pro Glu Lys Ser Lys Leu Pro
340 345 350

5 Gly Ile Val Ala Glu Gly Arg Asp Asp Leu Tyr Val Ser Asp Ala Phe
355 360 365

10 His Lys Ala Phe Leu Glu Val Asn Glu Glu Gly Ser Glu Ala Ala Ala
370 375 380

15 Ser Thr Ala Val Val Ile Ala Gly Arg Leu Asn Pro Asn Arg Val Thr
385 390 395 400

20 Phe Lys Ala Asn Arg Pro Phe Leu Val Phe Ile Arg Glu Val Pro Leu
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25 Asn Thr Ile Ile Phe Met Gly Arg Val Ala Asn Pro Cys Val Lys
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	Met	Asn	Pro	Met	Cys	Ile	Tyr	Arg	Ser	Pro	Glu	Lys	Lys	Ala	Thr	Glu	
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10	gat	gag	ggc	tca	gaa	cag	aag	atc	ccg	gag	gcc	acc	aac	cgg	cgt	gtc	144
	Asp	Glu	Gly	Ser	Glu	Gln	Lys	Ile	Pro	Glu	Ala	Thr	Asn	Arg	Arg	Val	
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15	tgg	gaa	ctg	tcc	aag	gcc	aat	tcc	cgc	ttt	gct	acc	act	ttc	tat	cag	192
	Trp	Glu	Leu	Ser	Lys	Ala	Asn	Ser	Arg	Phe	Ala	Thr	Thr	Phe	Tyr	Gln	
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25	ctg	agt	atc	tcc	acg	gct	ttt	gct	atg	acc	aag	ctg	ggg	gcc	tgt	aat	288
	Leu	Ser	Ile	Ser	Thr	Ala	Phe	Ala	Met	Thr	Lys	Leu	Gly	Ala	Cys	Asn	
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	Glu	Lys	Thr	Ser	Asp	Gln	Ile	His	Phe	Phe	Phe	Ala	Lys	Leu	Asn	Cys	
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	Ile	Ser	Glu	Leu	Val	Tyr	Gly	Ala	Lys	Leu	Gln	Pro	Leu	Asp	Phe	Lys	
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5 Met Asn Pro Met Cys Ile Tyr Arg Ser Pro Glu Lys Lys Ala Thr Glu
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10 Asp Glu Gly Ser Glu Gln Lys Ile Pro Glu Ala Thr Asn Arg Arg Val
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15 Trp Glu Leu Ser Lys Ala Asn Ser Arg Phe Ala Thr Thr Phe Tyr Gln
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20 His Leu Ala Asp Ser Lys Asn Asp Asn Asp Asn Ile Phe Leu Ser Pro
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25 Leu Ser Ile Ser Thr Ala Phe Ala Met Thr Lys Leu Gly Ala Cys Asn
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Asp Thr Leu Gln Gln Leu Met Glu Val Phe Lys Phe Asp Thr Ile Ser

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20	Ile Ser Glu Leu Val Tyr Gly Ala Lys Leu Gln Pro Leu Asp Phe Lys 165 170 175		
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30	Lys Thr Glu Gly Arg Ile Thr Asp Val Ile Pro Ser Glu Ala Ile Asn 195 200 205		
35	Glu Leu Thr Val Leu Val Leu Val Asn Thr Ile Tyr Phe Lys Gly Leu 210 215 220		
40	Trp Lys Ser Lys Phe Ser Pro Glu Asn Thr Arg Lys Glu Leu Phe Tyr 225 230 235 240		
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	Glu Lys Ser Leu Ala Lys Val Glu Lys Glu Leu Thr Pro Glu Val Leu 290 295 300		
	Gln Glu Trp Leu Asp Glu Leu Glu Glu Met Met Leu Val Val His Met 305 310 315 320		
	Pro Arg Phe Arg Ile Glu Asp Gly Phe Ser Leu Lys Glu Gln Leu Gln 325 330 335		
	Asp Met Gly Leu Val Asp Leu Phe Ser Pro Glu Lys Ser Lys Leu Pro		

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5 Gly Ile Val Ala Glu Gly Arg Asp Asp Leu Tyr Val Ser Asp Ala Phe
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10 His Lys Ala Phe Leu Glu Val Asn Glu Glu Gly Ser Glu Ala Ala Ala
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15 Ser Thr Ala Val Val Ile Ala Gly Leu Asn Pro Asn Arg Val Thr Phe
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	Arg	Leu	Tyr	Arg	Lys	Ala	Asn	Lys	Ser	Ser	Lys	Leu	Val	Ser	Ala	Asn						
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	Glu	Asn	Ala	Glu	Gln	Ser	Arg	Ala	Ala	Ile	Asn	Lys	Trp	Val	Ser	Asn						
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	Lys	Thr	Glu	Gly	Arg	Ile	Thr	Asp	Val	Ile	Pro	Ser	Glu	Ala	Ile	Asn						
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20	cat aag gca ttt ctt gag gta aat gaa gaa ggc agt gaa gca gct gca His Lys Ala Phe Leu Glu Val Asn Glu Glu Gly Ser Glu Ala Ala Ala 405 410 415	1248		
25	agt acc gct gtt gtg att gct ggc cgt tgc cta aac ccc aac agg gtg Ser Thr Ala Val Val Ile Ala Gly Arg Ser Leu Asn Pro Asn Arg Val 420 425 430	1296		
30	act ttc aag gcc aac agg cct ttc ctg gtt ttt ata aga gaa gtt cct Thr Phe Lys Ala Asn Arg Pro Phe Leu Val Phe Ile Arg Glu Val Pro 435 440 445	1344		
35	ctg aac act att atc ttc atg ggc aga gta gcc aac cct tgt gtt aag Leu Asn Thr Ile Ile Phe Met Gly Arg Val Ala Asn Pro Cys Val Lys 450 455 460	1392		
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5 Tyr Leu Leu Ser Leu Leu Leu Ile Gly Phe Trp Asp Cys Val Thr Cys
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10 His Gly Ser Pro Val Asp Ile Cys Thr Ala Lys Pro Arg Asp Ile Pro
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15 Met Asn Pro Met Cys Ile Tyr Arg Ser Pro Glu Lys Lys Ala Thr Glu
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20 Asp Glu Gly Ser Glu Gln Lys Ile Pro Glu Ala Thr Asn Arg Arg Val
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	Trp	Glu	Leu	Ser	Lys	Ala	Asn	Ser	Arg	Phe	Ala	Thr	Thr	Phe	Tyr	Gln	
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	His	Leu	Ala	Asp	Ser	Lys	Asn	Asp	Asn	Asp	Asn	Ile	Phe	Leu	Ser	Pro	
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	Leu	Ser	Ile	Ser	Thr	Ala	Phe	Ala	Met	Thr	Lys	Leu	Gly	Ala	Cys	Asn	
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	Asp	Thr	Leu	Gln	Gln	Leu	Met	Glu	Val	Phe	Lys	Phe	Asp	Thr	Ile	Ser	
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	Glu	Lys	Thr	Ser	Asp	Gln	Ile	His	Phe	Phe	Phe	Ala	Lys	Leu	Asn	Cys	
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	Arg	Leu	Tyr	Arg	Lys	Ala	Asn	Lys	Ser	Ser	Lys	Leu	Val	Ser	Ala	Asn	
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	Arg	Leu	Phe	Gly	Asp	Lys	Ser	Leu	Thr	Phe	Asn	Glu	Thr	Tyr	Gln	Asp	
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	Ile	Ser	Glu	Leu	Val	Tyr	Gly	Ala	Lys	Leu	Gln	Pro	Leu	Asp	Phe	Lys	
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	Trp	Lys	Ser	Lys	Phe	Ser	Pro	Glu	Asn	Thr	Arg	Lys	Glu	Leu	Phe	Tyr	
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	Lys	Ala	Asp	Gly	Glu	Ser	Cys	Ser	Ala	Ser	Met	Met	Tyr	Gln	Glu	Gly	
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	Gln Glu Trp Leu Asp Glu Leu Glu Glu Met Met Leu Val Val His Met	
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	Pro Arg Phe Arg Ile Glu Asp Gly Phe Ser Leu Lys Glu Gln Leu Gln	
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	Asp Met Gly Leu Val Asp Leu Phe Ser Pro Glu Lys Ser Lys Leu Pro	
	370 375 380	
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	Gly Ile Val Ala Glu Gly Arg Asp Asp Leu Tyr Val Ser Asp Ala Phe	
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	His Lys Ala Phe Leu Glu Val Asn Glu Glu Gly Ser Glu Ala Ala Ala	
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40	agt acc gct gtt gtg att gct ggc cat tcg cta aac ccc aac agg gtg	1296
	Ser Thr Ala Val Val Ile Ala Gly His Ser Leu Asn Pro Asn Arg Val	
	420 425 430	
45	act ttc aag gcc aac agg cct ttc ctg gtt ttt ata aga gaa gtt cct	1344
	Thr Phe Lys Ala Asn Arg Pro Phe Leu Val Phe Ile Arg Glu Val Pro	
	435 440 445	
50	ctg aac act att atc ttc atg ggc aga gta gcc aac cct tgt gtt aag	1392
	Leu Asn Thr Ile Ile Phe Met Gly Arg Val Ala Asn Pro Cys Val Lys	
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40	Gly	Ile	Val	Ala	Glu	Gly	Arg	Asp	Asp	Leu	Tyr	Val	Ser	Asp	Ala	Phe
	385					390					395					400
45	His	Lys	Ala	Phe	Leu	Glu	Val	Asn	Glu	Glu	Gly	Ser	Glu	Ala	Ala	Ala
					405					410					415	
50	Ser	Thr	Ala	Val	Val	Ile	Ala	Gly	His	Ser	Leu	Asn	Pro	Asn	Arg	Val
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55	Thr	Phe	Lys	Ala	Asn	Arg	Pro	Phe	Leu	Val	Phe	Ile	Arg	Glu	Val	Pro
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	Met	Asn	Pro	Met	Cys	Ile	Tyr	Arg	Ser	Pro	Glu	Lys	Lys	Ala	Thr	Glu	
		50					55					60					
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	Asp	Glu	Gly	Ser	Glu	Gln	Lys	Ile	Pro	Glu	Ala	Thr	Asn	Arg	Arg	Val	
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	Trp	Glu	Leu	Ser	Lys	Ala	Asn	Ser	Arg	Phe	Ala	Thr	Thr	Phe	Tyr	Gln	
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	His	Leu	Ala	Asp	Ser	Lys	Asn	Asp	Asn	Asp	Asn	Ile	Phe	Leu	Ser	Pro	
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	Leu	Ser	Ile	Ser	Thr	Ala	Phe	Ala	Met	Thr	Lys	Leu	Gly	Ala	Cys	Asn	
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	Arg	Leu	Tyr	Arg	Lys	Ala	Asn	Lys	Ser	Ser	Lys	Leu	Val	Ser	Ala	Asn	
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	Arg	Leu	Phe	Gly	Asp	Lys	Ser	Leu	Thr	Phe	Asn	Glu	Thr	Tyr	Gln	Asp	
			180					185						190			
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	Ile	Ser	Glu	Leu	Val	Tyr	Gly	Ala	Lys	Leu	Gln	Pro	Leu	Asp	Phe	Lys	
			195				200						205				
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10	tgg aag tca aag ttc agc cct gag aac aca agg aag gaa ctg ttc tac	816
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	His Lys Ala Phe Leu Glu Val Asn Glu Glu Gly Ser Glu Ala Ala Ala	
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	agt acc gct gtt gtg att gct ggc cgt cca tcg cta aac ccc aac agg	1296
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50	gtg act ttc aag gcc aac agg cct ttc ctg gtt ttt ata aga gaa gtt	1344
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55	cct ctg aac act att atc ttc atg ggc aga gta gcc aac cct tgt gtt	1392
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40	Glu	Lys	Ser	Leu	Ala	Lys	Val	Glu	Lys	Glu	Leu	Thr	Pro	Glu	Val	Leu
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30	tat ctt ttg tcc ttg ctg ctc att ggc ttc tgg gac tgc gtg acc tgt	96
	Tyr Leu Leu Ser Leu Leu Leu Ile Gly Phe Trp Asp Cys Val Thr Cys	
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35	cac ggg agc cct gtg gac atc tgc aca gcc aag ccg cgg gac att ccc	144
	His Gly Ser Pro Val Asp Ile Cys Thr Ala Lys Pro Arg Asp Ile Pro	
	35 40 45	
40	atg aat ccc atg tgc att tac cgc tcc ccg gag aag aag gca act gag	192
	Met Asn Pro Met Cys Ile Tyr Arg Ser Pro Glu Lys Lys Ala Thr Glu	
	50 55 60	
45	gat gag ggc tca gaa cag aag atc ccg gag gcc acc aac cgg cgt gtc	240
	Asp Glu Gly Ser Glu Gln Lys Ile Pro Glu Ala Thr Asn Arg Arg Val	
	65 70 75 80	
50	tgg gaa ctg tcc aag gcc aat tcc cgc ttt gct acc act ttc tat cag	288
	Trp Glu Leu Ser Lys Ala Asn Ser Arg Phe Ala Thr Thr Phe Tyr Gln	
	85 90 95	
55	cac ctg gca gat tcc aag aat gac aat gat aac att ttc ctg tca ccc	336
	His Leu Ala Asp Ser Lys Asn Asp Asn Asp Asn Ile Phe Leu Ser Pro	
	100 105 110	
60	ctg agt atc tcc acg gct ttt gct atg acc aag ctg ggt gcc tgt aat	384
	Leu Ser Ile Ser Thr Ala Phe Ala Met Thr Lys Leu Gly Ala Cys Asn	
	115 120 125	
65	gac acc ctc cag caa ctg atg gag gta ttt aag ttt gac acc ata tct	432
	Asp Thr Leu Gln Gln Leu Met Glu Val Phe Lys Phe Asp Thr Ile Ser	
	130 135 140	

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		gag	aaa	aca	tct	gat	cag	atc	cac	ttc	ttc	ttt	gcc	aaa	ctg	aac	tgc	480
		Glu	Lys	Thr	Ser	Asp	Gln	Ile	His	Phe	Phe	Phe	Ala	Lys	Leu	Asn	Cys	
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5		cga	ctc	tat	cga	aaa	gcc	aac	aaa	tcc	tcc	aag	tta	gta	tca	gcc	aat	528
		Arg	Leu	Tyr	Arg	Lys	Ala	Asn	Lys	Ser	Ser	Lys	Leu	Val	Ser	Ala	Asn	
						165					170					175		
10		cgc	ctt	ttt	gga	gac	aaa	tcc	ctt	acc	ttc	aat	gag	acc	tac	cag	gac	576
		Arg	Leu	Phe	Gly	Asp	Lys	Ser	Leu	Thr	Phe	Asn	Glu	Thr	Tyr	Gln	Asp	
					180					185					190			
15		atc	agt	gag	ttg	gta	tat	gga	gcc	aag	ctc	cag	ccc	ctg	gac	ttc	aag	624
		Ile	Ser	Glu	Leu	Val	Tyr	Gly	Ala	Lys	Leu	Gln	Pro	Leu	Asp	Phe	Lys	
				195				200					205					
20		gaa	aat	gca	gag	caa	tcc	aga	gcg	gcc	atc	aac	aaa	tgg	gtg	tcc	aat	672
		Glu	Asn	Ala	Glu	Gln	Ser	Arg	Ala	Ala	Ile	Asn	Lys	Trp	Val	Ser	Asn	
			210					215					220					
25		aag	acc	gaa	ggc	cga	atc	acc	gat	gtc	att	ccc	tcg	gaa	gcc	atc	aat	720
		Lys	Thr	Glu	Gly	Arg	Ile	Thr	Asp	Val	Ile	Pro	Ser	Glu	Ala	Ile	Asn	
		225					230					235					240	
30		gag	ctc	act	gtt	ctg	gtg	ctg	gtt	aac	acc	att	tac	ttc	aag	ggc	ctg	768
		Glu	Leu	Thr	Val	Leu	Val	Leu	Val	Asn	Thr	Ile	Tyr	Phe	Lys	Gly	Leu	
					245					250						255		
35		tgg	aag	tca	aag	ttc	agc	cct	gag	aac	aca	agg	aag	gaa	ctg	ttc	tac	816
		Trp	Lys	Ser	Lys	Phe	Ser	Pro	Glu	Asn	Thr	Arg	Lys	Glu	Leu	Phe	Tyr	
					260					265					270			
40		aag	gct	gat	gga	gag	tcg	tgt	tca	gca	tct	atg	atg	tac	cag	gaa	ggc	864
		Lys	Ala	Asp	Gly	Glu	Ser	Cys	Ser	Ala	Ser	Met	Met	Tyr	Gln	Glu	Gly	
				275				280						285				
45		aag	ttc	cgt	tat	cgg	cgc	gtg	gct	gaa	ggc	acc	cag	gtg	ctt	gag	ttg	912
		Lys	Phe	Arg	Tyr	Arg	Arg	Val	Ala	Glu	Gly	Thr	Gln	Val	Leu	Glu	Leu	
			290					295					300					
50		ccc	ttc	aaa	ggt	gat	gac	atc	acc	atg	gtc	ctc	atc	ttg	ccc	aag	cct	960
		Pro	Phe	Lys	Gly	Asp	Asp	Ile	Thr	Met	Val	Leu	Ile	Leu	Pro	Lys	Pro	
		305				310						315					320	
55		gag	aag	agc	ctg	gcc	aag	gta	gag	aag	gaa	ctc	acc	cca	gag	gtg	ctg	1008
		Glu	Lys	Ser	Leu	Ala	Lys	Val	Glu	Lys	Glu	Leu	Thr	Pro	Glu	Val	Leu	
					325					330						335		
60		caa	gag	tgg	ctg	gat	gaa	ttg	gag	gag	atg	atg	ctg	gtg	gtc	cac	atg	1056
		Gln	Glu	Trp	Leu	Asp	Glu	Leu	Glu	Glu	Met	Met	Leu	Val	Val	His	Met	
					340					345					350			
65		ccc	cgc	ttc	cgc	att	gag	gac	ggc	ttc	agt	ttg	aag	gag	cag	ctg	caa	1104
		Pro	Arg	Phe	Arg	Ile	Glu	Asp	Gly	Phe	Ser	Leu	Lys	Glu	Gln	Leu	Gln	
				355					360					365				
70		gac	atg	ggc	ctt	gtc	gat	ctg	ttc	agc	cct	gaa	aag	tcc	aaa	ctc	cca	1152
		Asp	Met	Gly	Leu	Val	Asp	Leu	Phe	Ser	Pro	Glu	Lys	Ser	Lys	Leu	Pro	
			370					375					380					

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	ggt att gtt gca gaa ggc cga gat gac ctc tat gtc tca gat gca ttc	1200
	Gly Ile Val Ala Glu Gly Arg Asp Asp Leu Tyr Val Ser Asp Ala Phe	
	385 390 395 400	
5	cat aag gca ttt ctt gag gta aat gaa gaa ggc agt gaa gca gct gca	1248
	His Lys Ala Phe Leu Glu Val Asn Glu Glu Gly Ser Glu Ala Ala Ala	
	405 410 415	
10	agt acc gct gtt gtg att gct ggc tcg cta aac ccc aac agg gtg act	1296
	Ser Thr Ala Val Val Ile Ala Gly Ser Leu Asn Pro Asn Arg Val Thr	
	420 425 430	
15	ttc aag gcc aac agg cct ttc ctg gtt ttt ata aga gaa gtt cct ctg	1344
	Phe Lys Ala Asn Arg Pro Phe Leu Val Phe Ile Arg Glu Val Pro Leu	
	435 440 445	
	aac act att atc ttc atg ggc aga gta gcc aac cct tgt gtt aag	1389
	Asn Thr Ile Ile Phe Met Gly Arg Val Ala Asn Pro Cys Val Lys	
	450 455 460	
20	taaaatgttc ttattctttg cacctcttcc tatttttggt ttgtgaacag aagtaaaaat	1449
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Met Tyr Ser Asn Val Ile Gly Thr Val Thr Ser Gly Lys Arg Lys Val
1 5 10 15

5 Tyr Leu Leu Ser Leu Leu Leu Ile Gly Phe Trp Asp Cys Val Thr Cys
20 25 30

10 His Gly Ser Pro Val Asp Ile Cys Thr Ala Lys Pro Arg Asp Ile Pro
35 40 45

15 Met Asn Pro Met Cys Ile Tyr Arg Ser Pro Glu Lys Lys Ala Thr Glu
50 55 60

20 Asp Glu Gly Ser Glu Gln Lys Ile Pro Glu Ala Thr Asn Arg Arg Val
65 70 75 80

25 Trp Glu Leu Ser Lys Ala Asn Ser Arg Phe Ala Thr Thr Phe Tyr Gln
85 90 95

30 His Leu Ala Asp Ser Lys Asn Asp Asn Asp Asn Ile Phe Leu Ser Pro
100 105 110

35

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	Leu	Ser	Ile	Ser	Thr	Ala	Phe	Ala	Met	Thr	Lys	Leu	Gly	Ala	Cys	Asn	
			115					120					125				
5	Asp	Thr	Leu	Gln	Gln	Leu	Met	Glu	Val	Phe	Lys	Phe	Asp	Thr	Ile	Ser	
		130					135					140					
10	Glu	Lys	Thr	Ser	Asp	Gln	Ile	His	Phe	Phe	Phe	Ala	Lys	Leu	Asn	Cys	
	145					150					155					160	
15	Arg	Leu	Tyr	Arg	Lys	Ala	Asn	Lys	Ser	Ser	Lys	Leu	Val	Ser	Ala	Asn	
					165					170					175		
20	Arg	Leu	Phe	Gly	Asp	Lys	Ser	Leu	Thr	Phe	Asn	Glu	Thr	Tyr	Gln	Asp	
				180					185					190			
25	Ile	Ser	Glu	Leu	Val	Tyr	Gly	Ala	Lys	Leu	Gln	Pro	Leu	Asp	Phe	Lys	
			195					200					205				
30	Glu	Asn	Ala	Glu	Gln	Ser	Arg	Ala	Ala	Ile	Asn	Lys	Trp	Val	Ser	Asn	
		210					215					220					
35	Lys	Thr	Glu	Gly	Arg	Ile	Thr	Asp	Val	Ile	Pro	Ser	Glu	Ala	Ile	Asn	
	225					230					235					240	
40	Glu	Leu	Thr	Val	Leu	Val	Leu	Val	Asn	Thr	Ile	Tyr	Phe	Lys	Gly	Leu	
					245					250					255		
45	Trp	Lys	Ser	Lys	Phe	Ser	Pro	Glu	Asn	Thr	Arg	Lys	Glu	Leu	Phe	Tyr	
				260					265					270			
50	Lys	Ala	Asp	Gly	Glu	Ser	Cys	Ser	Ala	Ser	Met	Met	Tyr	Gln	Glu	Gly	
			275					280					285				
55	Lys	Phe	Arg	Tyr	Arg	Arg	Val	Ala	Glu	Gly	Thr	Gln	Val	Leu	Glu	Leu	
		290					295					300					
60	Pro	Phe	Lys	Gly	Asp	Asp	Ile	Thr	Met	Val	Leu	Ile	Leu	Pro	Lys	Pro	
	305					310					315					320	
65	Glu	Lys	Ser	Leu	Ala	Lys	Val	Glu	Lys	Glu	Leu	Thr	Pro	Glu	Val	Leu	
					325					330					335		
70	Gln	Glu	Trp	Leu	Asp	Glu	Leu	Glu	Glu	Met	Met	Leu	Val	Val	His	Met	
				340					345					350			

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Pro Arg Phe Arg Ile Glu Asp Gly Phe Ser Leu Lys Glu Gln Leu Gln
355 360 365

5 Asp Met Gly Leu Val Asp Leu Phe Ser Pro Glu Lys Ser Lys Leu Pro
370 375 380

10 Gly Ile Val Ala Glu Gly Arg Asp Asp Leu Tyr Val Ser Asp Ala Phe
385 390 395 400

15 His Lys Ala Phe Leu Glu Val Asn Glu Glu Gly Ser Glu Ala Ala Ala
405 410 415

20 Ser Thr Ala Val Val Ile Ala Gly Ser Leu Asn Pro Asn Arg Val Thr
420 425 430

25 Phe Lys Ala Asn Arg Pro Phe Leu Val Phe Ile Arg Glu Val Pro Leu
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30 Asn Thr Ile Ile Phe Met Gly Arg Val Ala Asn Pro Cys Val Lys
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5	tat	ctt	ttg	tcc	ttg	ctg	ctc	att	ggc	ttc	tgg	gac	tgc	gtg	acc	tgt	96
	Tyr	Leu	Leu	Ser	Leu	Leu	Leu	Ile	Gly	Phe	Trp	Asp	Cys	Val	Thr	Cys	
				20					25					30			
10	cac	ggg	agc	cct	gtg	gac	atc	tgc	aca	gcc	aag	ccg	cgg	gac	att	ccc	144
	His	Gly	Ser	Pro	Val	Asp	Ile	Cys	Thr	Ala	Lys	Pro	Arg	Asp	Ile	Pro	
			35					40					45				
15	atg	aat	ccc	atg	tgc	att	tac	cgc	tcc	ccg	gag	aag	aag	gca	act	gag	192
	Met	Asn	Pro	Met	Cys	Ile	Tyr	Arg	Ser	Pro	Glu	Lys	Lys	Ala	Thr	Glu	
		50					55					60					
20	gat	gag	ggc	tca	gaa	cag	aag	atc	ccg	gag	gcc	acc	aac	cgg	cgt	gtc	240
	Asp	Glu	Gly	Ser	Glu	Gln	Lys	Ile	Pro	Glu	Ala	Thr	Asn	Arg	Arg	Val	
	65					70					75					80	
25																	
30																	
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	tgg gaa ctg tcc aag gcc aat tcc cgc ttt gct acc act ttc tat cag	288
	Trp Glu Leu Ser Lys Ala Asn Ser Arg Phe Ala Thr Thr Phe Tyr Gln	
	85 90 95	
5	cac ctg gca gat tcc aag aat gac aat gat aac att ttc ctg tca ccc	336
	His Leu Ala Asp Ser Lys Asn Asp Asn Asp Asn Ile Phe Leu Ser Pro	
	100 105 110	
10	ctg agt atc tcc acg gct ttt gct atg acc aag ctg ggt gcc tgt aat	384
	Leu Ser Ile Ser Thr Ala Phe Ala Met Thr Lys Leu Gly Ala Cys Asn	
	115 120 125	
15	gac acc ctc cag caa ctg atg gag gta ttt aag ttt gac acc ata tct	432
	Asp Thr Leu Gln Gln Leu Met Glu Val Phe Lys Phe Asp Thr Ile Ser	
	130 135 140	
20	gag aaa aca tct gat cag atc cac ttc ttc ttt gcc aaa ctg aac tgc	480
	Glu Lys Thr Ser Asp Gln Ile His Phe Phe Phe Ala Lys Leu Asn Cys	
	145 150 155 160	
25	cga ctc tat cga aaa gcc aac aaa tcc tcc aag tta gta tca gcc aat	528
	Arg Leu Tyr Arg Lys Ala Asn Lys Ser Ser Lys Leu Val Ser Ala Asn	
	165 170 175	
30	cgc ctt ttt gga gac aaa tcc ctt acc ttc aat gag acc tac cag gac	576
	Arg Leu Phe Gly Asp Lys Ser Leu Thr Phe Asn Glu Thr Tyr Gln Asp	
	180 185 190	
35	atc agt gag ttg gta tat gga gcc aag ctc cag ccc ctg gac ttc aag	624
	Ile Ser Glu Leu Val Tyr Gly Ala Lys Leu Gln Pro Leu Asp Phe Lys	
	195 200 205	
40	gaa aat gca gag caa tcc aga gcg gcc atc aac aaa tgg gtg tcc aat	672
	Glu Asn Ala Glu Gln Ser Arg Ala Ala Ile Asn Lys Trp Val Ser Asn	
	210 215 220	
45	aag acc gaa ggc cga atc acc gat gtc att ccc tcg gaa gcc atc aat	720
	Lys Thr Glu Gly Arg Ile Thr Asp Val Ile Pro Ser Glu Ala Ile Asn	
	225 230 235 240	
50	gag ctc act gtt ctg gtg ctg gtt aac acc att tac ttc aag ggc ctg	768
	Glu Leu Thr Val Leu Val Leu Val Asn Thr Ile Tyr Phe Lys Gly Leu	
	245 250 255	
55	tgg aag tca aag ttc agc cct gag aac aca agg aag gaa ctg ttc tac	816
	Trp Lys Ser Lys Phe Ser Pro Glu Asn Thr Arg Lys Glu Leu Phe Tyr	
	260 265 270	
60	aag gct gat gga gag tcg tgt tca gca tct atg atg tac cag gaa ggc	864
	Lys Ala Asp Gly Glu Ser Cys Ser Ala Ser Met Met Tyr Gln Glu Gly	
	275 280 285	
65	aag ttc cgt tat cgg cgc gtg gct gaa ggc acc cag gtg ctt gag ttg	912
	Lys Phe Arg Tyr Arg Arg Val Ala Glu Gly Thr Gln Val Leu Glu Leu	
	290 295 300	
70	ccc ttc aaa ggt gat gac atc acc atg gtc ctc atc ttg ccc aag cct	960
	Pro Phe Lys Gly Asp Asp Ile Thr Met Val Leu Ile Leu Pro Lys Pro	
	305 310 315 320	

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	gag aag agc ctg gcc aag gta gag aag gaa ctc acc cca gag gtg ctg	1008
	Glu Lys Ser Leu Ala Lys Val Glu Lys Glu Leu Thr Pro Glu Val Leu	
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5	caa gag tgg ctg gat gaa ttg gag gag atg atg ctg gtg gtc cac atg	1056
	Gln Glu Trp Leu Asp Glu Leu Glu Glu Met Met Leu Val Val His Met	
	340 345 350	
10	ccc cgc ttc cgc att gag gac ggc ttc agt ttg aag gag cag ctg caa	1104
	Pro Arg Phe Arg Ile Glu Asp Gly Phe Ser Leu Lys Glu Gln Leu Gln	
	355 360 365	
15	gac atg ggc ctt gtc gat ctg ttc agc cct gaa aag tcc aaa ctc cca	1152
	Asp Met Gly Leu Val Asp Leu Phe Ser Pro Glu Lys Ser Lys Leu Pro	
	370 375 380	
20	ggt att gtt gca gaa ggc cga gat gac ctc tat gtc tca gat gca ttc	1200
	Gly Ile Val Ala Glu Gly Arg Asp Asp Leu Tyr Val Ser Asp Ala Phe	
	385 390 395 400	
25	cat aag gca ttt ctt gag gta aat gaa gaa ggc agt gaa gca gct gca	1248
	His Lys Ala Phe Leu Glu Val Asn Glu Glu Gly Ser Glu Ala Ala Ala	
	405 410 415	
30	agt acc gct gtt gtg att gct ggc cgt cta aac ccc aac agg gtg act	1296
	Ser Thr Ala Val Val Ile Ala Gly Arg Leu Asn Pro Asn Arg Val Thr	
	420 425 430	
35	ttc aag gcc aac agg cct ttc ctg gtt ttt ata aga gaa gtt cct ctg	1344
	Phe Lys Ala Asn Arg Pro Phe Leu Val Phe Ile Arg Glu Val Pro Leu	
	435 440 445	
40	aac act att atc ttc atg ggc aga gta gcc aac cct tgt gtt aag	1389
	Asn Thr Ile Ile Phe Met Gly Arg Val Ala Asn Pro Cys Val Lys	
	450 455 460	
45	taaaatgttc ttattctttg cacctcttcc tatttttgggt ttgtgaacag aagtaaaaat	1449
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	20 25 30	
	His Gly Ser Pro Val Asp Ile Cys Thr Ala Lys Pro Arg Asp Ile Pro	
	35 40 45	

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	Met	Asn	Pro	Met	Cys	Ile	Tyr	Arg	Ser	Pro	Glu	Lys	Lys	Ala	Thr	Glu
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10	Trp	Glu	Leu	Ser	Lys	Ala	Asn	Ser	Arg	Phe	Ala	Thr	Thr	Phe	Tyr	Gln
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15	His	Leu	Ala	Asp	Ser	Lys	Asn	Asp	Asn	Asp	Asn	Ile	Phe	Leu	Ser	Pro
				100					105					110		
20	Leu	Ser	Ile	Ser	Thr	Ala	Phe	Ala	Met	Thr	Lys	Leu	Gly	Ala	Cys	Asn
			115					120					125			
25	Asp	Thr	Leu	Gln	Gln	Leu	Met	Glu	Val	Phe	Lys	Phe	Asp	Thr	Ile	Ser
	130						135						140			
30	Glu	Lys	Thr	Ser	Asp	Gln	Ile	His	Phe	Phe	Phe	Ala	Lys	Leu	Asn	Cys
	145					150					155					160
35	Arg	Leu	Tyr	Arg	Lys	Ala	Asn	Lys	Ser	Ser	Lys	Leu	Val	Ser	Ala	Asn
					165					170					175	
40	Arg	Leu	Phe	Gly	Asp	Lys	Ser	Leu	Thr	Phe	Asn	Glu	Thr	Tyr	Gln	Asp
				180					185					190		
45	Ile	Ser	Glu	Leu	Val	Tyr	Gly	Ala	Lys	Leu	Gln	Pro	Leu	Asp	Phe	Lys
			195					200					205			
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	210						215					220				
55	Lys	Thr	Glu	Gly	Arg	Ile	Thr	Asp	Val	Ile	Pro	Ser	Glu	Ala	Ile	Asn
	225					230					235					240
60	Glu	Leu	Thr	Val	Leu	Val	Leu	Val	Asn	Thr	Ile	Tyr	Phe	Lys	Gly	Leu
					245					250					255	
65	Trp	Lys	Ser	Lys	Phe	Ser	Pro	Glu	Asn	Thr	Arg	Lys	Glu	Leu	Phe	Tyr
				260					265					270		
70	Lys	Ala	Asp	Gly	Glu	Ser	Cys	Ser	Ala	Ser	Met	Met	Tyr	Gln	Glu	Gly
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Lys Phe Arg Tyr Arg Arg Val Ala Glu Gly Thr Gln Val Leu Glu Leu
290 295 300

5 Pro Phe Lys Gly Asp Asp Ile Thr Met Val Leu Ile Leu Pro Lys Pro
305 310 315 320

10 Glu Lys Ser Leu Ala Lys Val Glu Lys Glu Leu Thr Pro Glu Val Leu
325 330 335

15 Gln Glu Trp Leu Asp Glu Leu Glu Glu Met Met Leu Val Val His Met
340 345 350

20 Pro Arg Phe Arg Ile Glu Asp Gly Phe Ser Leu Lys Glu Gln Leu Gln
355 360 365

25 Asp Met Gly Leu Val Asp Leu Phe Ser Pro Glu Lys Ser Lys Leu Pro
370 375 380

30 Gly Ile Val Ala Glu Gly Arg Asp Asp Leu Tyr Val Ser Asp Ala Phe
385 390 395 400

35 His Lys Ala Phe Leu Glu Val Asn Glu Glu Gly Ser Glu Ala Ala Ala
405 410 415

40 Ser Thr Ala Val Val Ile Ala Gly Arg Leu Asn Pro Asn Arg Val Thr
420 425 430

45 Phe Lys Ala Asn Arg Pro Phe Leu Val Phe Ile Arg Glu Val Pro Leu
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Asn Thr Ile Ile Phe Met Gly Arg Val Ala Asn Pro Cys Val Lys
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<400> 35

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1				5					10					15		

5	tat	ctt	ttg	tcc	ttg	ctg	ctc	att	ggc	ttc	tgg	gac	tgc	gtg	acc	tgt	96
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	Tyr	Leu	Leu	Ser	Leu	Leu	Leu	Ile	Gly	Phe	Trp	Asp	Cys	Val	Thr	Cys	
				20					25					30			
5	cac	ggg	agc	cct	gtg	gac	atc	tgc	aca	gcc	aag	ccg	cgg	gac	att	ccc	144
	His	Gly	Ser	Pro	Val	Asp	Ile	Cys	Thr	Ala	Lys	Pro	Arg	Asp	Ile	Pro	
			35				40					45					
10	atg	aat	ccc	atg	tgc	att	tac	cgc	tcc	ccg	gag	aag	aag	gca	act	gag	192
	Met	Asn	Pro	Met	Cys	Ile	Tyr	Arg	Ser	Pro	Glu	Lys	Lys	Ala	Thr	Glu	
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	Asp	Glu	Gly	Ser	Glu	Gln	Lys	Ile	Pro	Glu	Ala	Thr	Asn	Arg	Arg	Val	
	65				70					75					80		
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	Trp	Glu	Leu	Ser	Lys	Ala	Asn	Ser	Arg	Phe	Ala	Thr	Thr	Phe	Tyr	Gln	
				85					90					95			
25	cac	ctg	gca	gat	tcc	aag	aat	gac	aat	gat	aac	att	ttc	ctg	tca	ccc	336
	His	Leu	Ala	Asp	Ser	Lys	Asn	Asp	Asn	Asp	Asn	Ile	Phe	Leu	Ser	Pro	
				100				105						110			
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	Leu	Ser	Ile	Ser	Thr	Ala	Phe	Ala	Met	Thr	Lys	Leu	Gly	Ala	Cys	Asn	
			115			120							125				
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	Asp	Thr	Leu	Gln	Gln	Leu	Met	Glu	Val	Phe	Lys	Phe	Asp	Thr	Ile	Ser	
		130				135						140					
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	Glu	Lys	Thr	Ser	Asp	Gln	Ile	His	Phe	Phe	Phe	Ala	Lys	Leu	Asn	Cys	
	145				150					155						160	
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	Arg	Leu	Tyr	Arg	Lys	Ala	Gln	Lys	Ser	Ser	Lys	Leu	Val	Ser	Ala	Asn	
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	Arg	Leu	Phe	Gly	Asp	Lys	Ser	Leu	Thr	Phe	Asn	Glu	Thr	Tyr	Gln	Asp	
			180					185						190			
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	Ile	Ser	Glu	Leu	Val	Tyr	Gly	Ala	Lys	Leu	Gln	Pro	Leu	Asp	Phe	Lys	
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	Lys	Thr	Glu	Gly	Arg	Ile	Thr	Asp	Val	Ile	Pro	Ser	Glu	Ala	Ile	Asn	
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	Glu	Leu	Thr	Val	Leu	Val	Leu	Val	Asn	Thr	Ile	Tyr	Phe	Lys	Gly	Leu	
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	Lys	Ala	Asp	Gly	Glu	Ser	Cys	Ser	Ala	Ser	Met	Met	Tyr	Gln	Glu	Gly	
			275					280					285				
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	Lys	Phe	Arg	Tyr	Arg	Arg	Val	Ala	Glu	Gly	Thr	Gln	Val	Leu	Glu	Leu	
		290					295					300					
15	ccc	ttc	aaa	ggg	gat	gac	atc	acc	atg	gtc	ctc	atc	ttg	ccc	aag	cct	960
	Pro	Phe	Lys	Gly	Asp	Asp	Ile	Thr	Met	Val	Leu	Ile	Leu	Pro	Lys	Pro	
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20	gag	aag	agc	ctg	gcc	aag	gta	gag	aag	gaa	ctc	acc	cca	gag	gtg	ctg	1008
	Glu	Lys	Ser	Leu	Ala	Lys	Val	Glu	Lys	Glu	Leu	Thr	Pro	Glu	Val	Leu	
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25	caa	gag	tgg	ctg	gat	gaa	ttg	gag	gag	atg	atg	ctg	gtg	gtc	cac	atg	1056
	Gln	Glu	Trp	Leu	Asp	Glu	Leu	Glu	Glu	Met	Met	Leu	Val	Val	His	Met	
			340					345					350				
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	Pro	Arg	Phe	Arg	Ile	Glu	Asp	Gly	Phe	Ser	Leu	Lys	Glu	Gln	Leu	Gln	
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	Asp	Met	Gly	Leu	Val	Asp	Leu	Phe	Ser	Pro	Glu	Lys	Ser	Lys	Leu	Pro	
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	His	Lys	Ala	Phe	Leu	Glu	Val	Asn	Glu	Glu	Gly	Ser	Glu	Ala	Ala	Ala	
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	Ser	Thr	Ala	Val	Val	Ile	Ala	Gly	Arg	Ser	Leu	Asn	Pro	Asn	Arg	Val	
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	Thr	Phe	Lys	Ala	Asn	Arg	Pro	Phe	Leu	Val	Phe	Ile	Arg	Glu	Val	Pro	
			435				440					445					
60	ctg	aac	act	att	atc	ttc	atg	ggc	aga	gta	gcc	aac	cct	tgt	gtt	aag	1392
	Leu	Asn	Thr	Ile	Ile	Phe	Met	Gly	Arg	Val	Ala	Asn	Pro	Cys	Val	Lys	
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			20						25					30		
10	His	Gly	Ser	Pro	Val	Asp	Ile	Cys	Thr	Ala	Lys	Pro	Arg	Asp	Ile	Pro
			35					40					45			
15	Met	Asn	Pro	Met	Cys	Ile	Tyr	Arg	Ser	Pro	Glu	Lys	Lys	Ala	Thr	Glu
		50					55					60				
20	Asp	Glu	Gly	Ser	Glu	Gln	Lys	Ile	Pro	Glu	Ala	Thr	Asn	Arg	Arg	Val
	65					70					75				80	
25	Trp	Glu	Leu	Ser	Lys	Ala	Asn	Ser	Arg	Phe	Ala	Thr	Thr	Phe	Tyr	Gln
				85						90					95	
30	His	Leu	Ala	Asp	Ser	Lys	Asn	Asp	Asn	Asp	Asn	Ile	Phe	Leu	Ser	Pro
			100					105						110		
35	Leu	Ser	Ile	Ser	Thr	Ala	Phe	Ala	Met	Thr	Lys	Leu	Gly	Ala	Cys	Asn
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40	Asp	Thr	Leu	Gln	Gln	Leu	Met	Glu	Val	Phe	Lys	Phe	Asp	Thr	Ile	Ser
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45	Glu	Lys	Thr	Ser	Asp	Gln	Ile	His	Phe	Phe	Phe	Ala	Lys	Leu	Asn	Cys
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50	Arg	Leu	Tyr	Arg	Lys	Ala	Gln	Lys	Ser	Ser	Lys	Leu	Val	Ser	Ala	Asn
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55	Arg	Leu	Phe	Gly	Asp	Lys	Ser	Leu	Thr	Phe	Asn	Glu	Thr	Tyr	Gln	Asp
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	225				230					235					240	
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10	Trp	Lys	Ser	Lys	Phe	Ser	Pro	Glu	Asn	Thr	Arg	Lys	Glu	Leu	Phe	Tyr
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15	Lys	Ala	Asp	Gly	Glu	Ser	Cys	Ser	Ala	Ser	Met	Met	Tyr	Gln	Glu	Gly
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		290					295					300				
25	Pro	Phe	Lys	Gly	Asp	Asp	Ile	Thr	Met	Val	Leu	Ile	Leu	Pro	Lys	Pro
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30	Glu	Lys	Ser	Leu	Ala	Lys	Val	Glu	Lys	Glu	Leu	Thr	Pro	Glu	Val	Leu
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35	Gln	Glu	Trp	Leu	Asp	Glu	Leu	Glu	Glu	Met	Met	Leu	Val	Val	His	Met
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40	Pro	Arg	Phe	Arg	Ile	Glu	Asp	Gly	Phe	Ser	Leu	Lys	Glu	Gln	Leu	Gln
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45	Asp	Met	Gly	Leu	Val	Asp	Leu	Phe	Ser	Pro	Glu	Lys	Ser	Lys	Leu	Pro
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55	His	Lys	Ala	Phe	Leu	Glu	Val	Asn	Glu	Glu	Gly	Ser	Glu	Ala	Ala	Ala
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60	Ser	Thr	Ala	Val	Val	Ile	Ala	Gly	Arg	Ser	Leu	Asn	Pro	Asn	Arg	Val
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65	Thr	Phe	Lys	Ala	Asn	Arg	Pro	Phe	Leu	Val	Phe	Ile	Arg	Glu	Val	Pro
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	tat Tyr	ctt Leu	ttg Leu	tcc Ser 20	ttg Leu	ctg Leu	ctc Leu	att Ile	ggc Gly 25	ttc Phe	tgg Trp	gac Asp	tgc Cys	gtg Val 30	acc Thr	tgt Cys	96
	cac His	ggg Gly	agc Ser 35	cct Pro	gtg Val	gac Asp	atc Ile	tgc Cys 40	aca Thr	gcc Ala	aag Lys	ccg Pro	cgg Arg 45	gac Asp	att Ile	ccc Pro	144
	atg Met 50	aat Asn	ccc Pro	atg Met	tgc Cys	att Ile	tac Tyr 55	cgc Arg	tcc Ser	ccg Pro	gag Glu 60	aag Lys	aag Lys	gca Ala	act Thr	gag Glu	192
	gat Asp 65	gag Glu	ggc Gly	tca Ser	gaa Glu 70	cag Gln	aag Lys	atc Ile	ccg Pro	gag Glu 75	gcc Ala	acc Thr	aac Asn	cgg Arg	cgt Arg 80	gtc Val	240
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	cac His	ctg Leu	gca Ala	gat Asp 100	tcc Ser	aag Lys	aat Asn	gac Asp 105	aat Asn	gat Asp	aac Asn	att Ile	ttc Phe	ctg Leu 110	tca Ser	ccc Pro	336
30	ctg Leu	agt Ser	atc Ile 115	tcc Ser	acg Thr	gct Ala	ttt Phe	gct Ala 120	atg Met	acc Thr	aag Lys	ctg Leu	ggt Gly 125	gcc Ala	tgt Cys	aat Asn	384
	gac Asp 130	acc Thr	ctc Leu	cag Gln	caa Gln	ctg Leu	atg Met 135	gag Glu	gta Val	ttt Phe	aag Lys	ttt Phe 140	gac Asp	acc Thr	ata Ile	tct Ser	432
35	gag Glu 145	aaa Lys	aca Thr	tct Ser	gat Asp 150	cag Gln	atc Ile	cac His	ttc Phe	ttc Phe	ttt Phe 155	gcc Ala	aaa Lys	ctg Leu	aac Asn	tgc Cys 160	480
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45	cgc Arg	ctt Leu	ttt Phe 180	gga Gly	gac Asp	aaa Lys	tcc Ser	ctt Leu	acc Thr 185	ttc Phe	aat Asn	gag Glu	acc Thr	tac Tyr 190	cag Gln	gac Asp	576
	atc Ile	agt Ser	gag Glu	ttg Leu	gta Val	tat Tyr	gga Gly	gcc Ala	aag Lys	ctc Leu	cag Gln	ccc Pro	ctg Leu	gac Asp	ttc Phe	aag Lys	624

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10	aag acc gaa ggc cga atc acc gat gtc att ccc tcg gaa gcc atc aat Lys Thr Glu Gly Arg Ile Thr Asp Val Ile Pro Ser Glu Ala Ile Asn 225 230 235 240			720
15	gag ctc act gtt ctg gtg ctg gtt aac acc att tac ttc aag ggc ctg Glu Leu Thr Val Leu Val Leu Val Asn Thr Ile Tyr Phe Lys Gly Leu 245 250 255			768
20	tgg aag tca aag ttc agc cct gag aac aca agg aag gaa ctg ttc tac Trp Lys Ser Lys Phe Ser Pro Glu Asn Thr Arg Lys Glu Leu Phe Tyr 260 265 270			816
25	aag gct gat gga gag tcg tgt tca gca tct atg atg tac cag gaa ggc Lys Ala Asp Gly Glu Ser Cys Ser Ala Ser Met Met Tyr Gln Glu Gly 275 280 285			864
30	aag ttc cgt tat cgg cgc gtg gct gaa ggc acc cag gtg ctt gag ttg Lys Phe Arg Tyr Arg Arg Val Ala Glu Gly Thr Gln Val Leu Glu Leu 290 295 300			912
35	ccc ttc aaa ggt gat gac atc acc atg gtc ctc atc ttg ccc aag cct Pro Phe Lys Gly Asp Asp Ile Thr Met Val Leu Ile Leu Pro Lys Pro 305 310 315 320			960
40	gag aag agc ctg gcc aag gta gag aag gaa ctc acc cca gag gtg ctg Glu Lys Ser Leu Ala Lys Val Glu Lys Glu Leu Thr Pro Glu Val Leu 325 330 335			1008
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55	gac atg ggc ctt gtc gat ctg ttc agc cct gaa aag tcc aaa ctc cca Asp Met Gly Leu Val Asp Leu Phe Ser Pro Glu Lys Ser Lys Leu Pro 370 375 380			1152
60	ggt att gtt gca gaa ggc cga gat gac ctc tat gtc tca gat gca ttc Gly Ile Val Ala Glu Gly Arg Asp Asp Leu Tyr Val Ser Asp Ala Phe 385 390 395 400			1200
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75	act ttc aag gcc aac agg cct ttc ctg gtt ttt ata aga gaa gtt cct Thr Phe Lys Ala Asn Arg Pro Phe Leu Val Phe Ile Arg Glu Val Pro 435 440 445 450			1344

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5 Tyr Leu Leu Ser Leu Leu Leu Ile Gly Phe Trp Asp Cys Val Thr Cys
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¹⁰ His Gly Ser Pro Val Asp Ile Cys Thr Ala Lys Pro Arg Asp Ile Pro
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20 Asp Glu Gly Ser Glu Gln Lys Ile Pro Glu Ala Thr Asn Arg Arg Val
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Trp Glu Leu Ser Lys Ala Asn Ser Arg Phe Ala Thr Thr Phe Tyr Gln
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His Leu Ala Asp Ser Lys Asn Asp Asn Asp Asn Ile Phe Leu Ser Pro
100 105 110

Leu Ser Ile Ser Thr Ala Phe Ala Met Thr Lys Leu Gly Ala Cys Asn
115 120 125

Asp Thr Leu Gln Gln Leu Met Glu Val Phe Lys Phe Asp Thr Ile Ser
130 135 140

Glu Lys Thr Ser Asp Gln Ile His Phe Phe Phe Ala Lys Leu Asn Cys
145 150 155 160

45 Arg Leu Tyr Arg Lys Ala Gln Lys Ser Ser Lys Leu Val Ser Ala Asn
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			355					360					365			
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	385					390					395					400
70	His	Lys	Ala	Phe	Leu	Glu	Val	Asn	Glu	Glu	Gly	Ser	Glu	Ala	Ala	Ala
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 420 425 430

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10 Leu Asn Thr Ile Ile Phe Met Gly Arg Val Ala Asn Pro Cys Val Lys
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 Tyr Leu Leu Ser Leu Leu Leu Ile Gly Phe Trp Asp Cys Val Thr Cys
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35 cac ggg agc cct gtg gac atc tgc aca gcc aag ccg cgg gac att ccc 144
 His Gly Ser Pro Val Asp Ile Cys Thr Ala Lys Pro Arg Asp Ile Pro
 35 40 45

atg aat ccc atg tgc att tac cgc tcc ccg gag aag aag gca act gag 192
 Met Asn Pro Met Cys Ile Tyr Arg Ser Pro Glu Lys Lys Ala Thr Glu
 50 55 60

40 gat gag ggc tca gaa cag aag atc ccg gag gcc acc aac cgg cgt gtc 240
 Asp Glu Gly Ser Glu Gln Lys Ile Pro Glu Ala Thr Asn Arg Arg Val
 65 70 75 80

45 tgg gaa ctg tcc aag gcc aat tcc cgc ttt gct acc act ttc tat cag 288
 Trp Glu Leu Ser Lys Ala Asn Ser Arg Phe Ala Thr Thr Phe Tyr Gln
 85 90 95

50 cac ctg gca gat tcc aag aat gac aat gat aac att ttc ctg tca ccc 336
 His Leu Ala Asp Ser Lys Asn Asp Asn Asp Asn Ile Phe Leu Ser Pro
 100 105 110

ctg agt atc tcc acg gct ttt gct atg acc aag ctg ggt gcc tgt aat 384
 Leu Ser Ile Ser Thr Ala Phe Ala Met Thr Lys Leu Gly Ala Cys Asn
 115 120 125

55 gac acc ctc cag caa ctg atg gag gta ttt aag ttt gac acc ata tct 432
 Asp Thr Leu Gln Gln Leu Met Glu Val Phe Lys Phe Asp Thr Ile Ser
 130 135 140

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		gag	aaa	aca	tct	gat	cag	atc	cac	ttc	ttc	ttt	gcc	aaa	ctg	aac	tgc	480
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		145					150					155					160	
5		cga	ctc	tat	cga	aaa	gcc	cag	aaa	tcc	tcc	aag	tta	gta	tca	gcc	aat	528
		Arg	Leu	Tyr	Arg	Lys	Ala	Gln	Lys	Ser	Ser	Lys	Leu	Val	Ser	Ala	Asn	
						165					170					175		
10		cgc	ctt	ttt	gga	gac	aaa	tcc	ctt	acc	ttc	aat	gag	acc	tac	cag	gac	576
		Arg	Leu	Phe	Gly	Asp	Lys	Ser	Leu	Thr	Phe	Asn	Glu	Thr	Tyr	Gln	Asp	
					180					185					190			
15		atc	agt	gag	ttg	gta	tat	gga	gcc	aag	ctc	cag	ccc	ctg	gac	ttc	aag	624
		Ile	Ser	Glu	Leu	Val	Tyr	Gly	Ala	Lys	Leu	Gln	Pro	Leu	Asp	Phe	Lys	
				195				200					205					
20		gaa	aat	gca	gag	caa	tcc	aga	gcg	gcc	atc	aac	aaa	tgg	gtg	tcc	aat	672
		Glu	Asn	Ala	Glu	Gln	Ser	Arg	Ala	Ala	Ile	Asn	Lys	Trp	Val	Ser	Asn	
			210					215					220					
25		aag	acc	gaa	ggc	cga	atc	acc	gat	gtc	att	ccc	tcg	gaa	gcc	atc	aat	720
		Lys	Thr	Glu	Gly	Arg	Ile	Thr	Asp	Val	Ile	Pro	Ser	Glu	Ala	Ile	Asn	
		225					230					235					240	
30		gag	ctc	act	gtt	ctg	gtg	ctg	gtt	aac	acc	att	tac	ttc	aag	ggc	ctg	768
		Glu	Leu	Thr	Val	Leu	Val	Leu	Val	Asn	Thr	Ile	Tyr	Phe	Lys	Gly	Leu	
						245					250					255		
35		tgg	aag	tca	aag	ttc	agc	cct	gag	aac	aca	agg	aag	gaa	ctg	ttc	tac	816
		Trp	Lys	Ser	Lys	Phe	Ser	Pro	Glu	Asn	Thr	Arg	Lys	Glu	Leu	Phe	Tyr	
					260					265					270			
40		aag	gct	gat	gga	gag	tcg	tgt	tca	gca	tct	atg	atg	tac	cag	gaa	ggc	864
		Lys	Ala	Asp	Gly	Glu	Ser	Cys	Ser	Ala	Ser	Met	Met	Tyr	Gln	Glu	Gly	
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45		aag	ttc	cgt	tat	cgg	cgc	gtg	gct	gaa	ggc	acc	cag	gtg	ctt	gag	ttg	912
		Lys	Phe	Arg	Tyr	Arg	Arg	Val	Ala	Glu	Gly	Thr	Gln	Val	Leu	Glu	Leu	
			290					295					300					
50		ccc	ttc	aaa	ggt	gat	gac	atc	acc	atg	gtc	ctc	atc	ttg	ccc	aag	cct	960
		Pro	Phe	Lys	Gly	Asp	Asp	Ile	Thr	Met	Val	Leu	Ile	Leu	Pro	Lys	Pro	
		305					310					315					320	
55		gag	aag	agc	ctg	gcc	aag	gta	gag	aag	gaa	ctc	acc	cca	gag	gtg	ctg	1008
		Glu	Lys	Ser	Leu	Ala	Lys	Val	Glu	Lys	Glu	Leu	Thr	Pro	Glu	Val	Leu	
						325					330					335		
60		caa	gag	tgg	ctg	gat	gaa	ttg	gag	gag	atg	atg	ctg	gtg	gtc	cac	atg	1056
		Gln	Glu	Trp	Leu	Asp	Glu	Leu	Glu	Glu	Met	Met	Leu	Val	Val	His	Met	
					340					345					350			
65		ccc	cgc	ttc	cgc	att	gag	gac	ggc	ttc	agt	ttg	aag	gag	cag	ctg	caa	1104
		Pro	Arg	Phe	Arg	Ile	Glu	Asp	Gly	Phe	Ser	Leu	Lys	Glu	Gln	Leu	Gln	
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70		gac	atg	ggc	ctt	gtc	gat	ctg	ttc	agc	cct	gaa	aag	tcc	aaa	ctc	cca	1152
		Asp	Met	Gly	Leu	Val	Asp	Leu	Phe	Ser	Pro	Glu	Lys	Ser	Lys	Leu	Pro	
			370					375					380					

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	ggt att gtt gca gaa ggc cga gat gac ctc tat gtc tca gat gca ttc	1200
	Gly Ile Val Ala Glu Gly Arg Asp Asp Leu Tyr Val Ser Asp Ala Phe	
	385 390 395 400	
5	cat aag gca ttt ctt gag gta aat gaa gaa ggc agt gaa gca gct gca	1248
	His Lys Ala Phe Leu Glu Val Asn Glu Glu Gly Ser Glu Ala Ala Ala	
	405 410 415	
10	agt acc gct gtt gtg att gct ggc cgt cca tcg cta aac ccc aac agg	1296
	Ser Thr Ala Val Val Ile Ala Gly Arg Pro Ser Leu Asn Pro Asn Arg	
	420 425 430	
15	gtg act ttc aag gcc aac agg cct ttc ctg gtt ttt ata aga gaa gtt	1344
	Val Thr Phe Lys Ala Asn Arg Pro Phe Leu Val Phe Ile Arg Glu Val	
	435 440 445	
20	cct ctg aac act att atc ttc atg ggc aga gta gcc aac cct tgt gtt	1392
	Pro Leu Asn Thr Ile Ile Phe Met Gly Arg Val Ala Asn Pro Cys Val	
	450 455 460	
25	aag taaaatgttc ttattctttg cacctcttcc tatttttggg ttgtgaacag	1445
	Lys	
	465	
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5 Tyr Leu Leu Ser Leu Leu Leu Ile Gly Phe Trp Asp Cys Val Thr Cys
20 25 30

10 His Gly Ser Pro Val Asp Ile Cys Thr Ala Lys Pro Arg Asp Ile Pro
35 40 45

15 Met Asn Pro Met Cys Ile Tyr Arg Ser Pro Glu Lys Lys Ala Thr Glu
50 55 60

20 Asp Glu Gly Ser Glu Gln Lys Ile Pro Glu Ala Thr Asn Arg Arg Val
65 70 75 80

25 Trp Glu Leu Ser Lys Ala Asn Ser Arg Phe Ala Thr Thr Phe Tyr Gln
85 90 95

His Leu Ala Asp Ser Lys Asn Asp Asn Asp Asn Ile Phe Leu Ser Pro

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	100		105		110
5	Leu Ser Ile Ser Thr Ala Phe Ala Met Thr Lys Leu Gly Ala Cys Asn	115	120	125	
10	Asp Thr Leu Gln Gln Leu Met Glu Val Phe Lys Phe Asp Thr Ile Ser	130	135	140	
15	Glu Lys Thr Ser Asp Gln Ile His Phe Phe Phe Ala Lys Leu Asn Cys	145	150	155	160
20	Arg Leu Tyr Arg Lys Ala Gln Lys Ser Ser Lys Leu Val Ser Ala Asn	165	170	175	
25	Arg Leu Phe Gly Asp Lys Ser Leu Thr Phe Asn Glu Thr Tyr Gln Asp	180	185	190	
30	Ile Ser Glu Leu Val Tyr Gly Ala Lys Leu Gln Pro Leu Asp Phe Lys	195	200	205	
35	Glu Asn Ala Glu Gln Ser Arg Ala Ala Ile Asn Lys Trp Val Ser Asn	210	215	220	
40	Lys Thr Glu Gly Arg Ile Thr Asp Val Ile Pro Ser Glu Ala Ile Asn	225	230	235	240
45	Glu Leu Thr Val Leu Val Leu Val Asn Thr Ile Tyr Phe Lys Gly Leu	245	250	255	
50	Trp Lys Ser Lys Phe Ser Pro Glu Asn Thr Arg Lys Glu Leu Phe Tyr	260	265	270	
55	Lys Ala Asp Gly Glu Ser Cys Ser Ala Ser Met Met Tyr Gln Glu Gly	275	280	285	
	Lys Phe Arg Tyr Arg Arg Val Ala Glu Gly Thr Gln Val Leu Glu Leu	290	295	300	
	Pro Phe Lys Gly Asp Asp Ile Thr Met Val Leu Ile Leu Pro Lys Pro	305	310	315	320
	Glu Lys Ser Leu Ala Lys Val Glu Lys Glu Leu Thr Pro Glu Val Leu	325	330	335	
	Gln Glu Trp Leu Asp Glu Leu Glu Glu Met Met Leu Val Val His Met				

340

345

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5 Pro Arg Phe Arg Ile Glu Asp Gly Phe Ser Leu Lys Glu Gln Leu Gln
355 360 365

10 Asp Met Gly Leu Val Asp Leu Phe Ser Pro Glu Lys Ser Lys Leu Pro
370 375 380

15 Gly Ile Val Ala Glu Gly Arg Asp Asp Leu Tyr Val Ser Asp Ala Phe
385 390 395 400

20 His Lys Ala Phe Leu Glu Val Asn Glu Glu Gly Ser Glu Ala Ala Ala
405 410 415

25 Ser Thr Ala Val Val Ile Ala Gly Arg Pro Ser Leu Asn Pro Asn Arg
420 425 430

30 Val Thr Phe Lys Ala Asn Arg Pro Phe Leu Val Phe Ile Arg Glu Val
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35 Pro Leu Asn Thr Ile Ile Phe Met Gly Arg Val Ala Asn Pro Cys Val
450 455 460

35 Lys
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	1				5					10					15		
5	tat	ctt	ttg	tcc	ttg	ctg	ctc	att	ggc	ttc	tgg	gac	tgc	gtg	acc	tgt	96
	Tyr	Leu	Leu	Ser	Leu	Leu	Leu	Ile	Gly	Phe	Trp	Asp	Cys	Val	Thr	Cys	
				20					25					30			
10	cac	ggg	agc	cct	gtg	gac	atc	tgc	aca	gcc	aag	ccg	cgg	gac	att	ccc	144
	His	Gly	Ser	Pro	Val	Asp	Ile	Cys	Thr	Ala	Lys	Pro	Arg	Asp	Ile	Pro	
			35					40					45				
15	atg	aat	ccc	atg	tgc	att	tac	cgc	tcc	ccg	gag	aag	aag	gca	act	gag	192
	Met	Asn	Pro	Met	Cys	Ile	Tyr	Arg	Ser	Pro	Glu	Lys	Lys	Ala	Thr	Glu	
20																	
25																	
30																	
35																	
40																	
45																	
50																	
55																	

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	50				55				60								
5	gat Asp 65	gag Glu	ggc Gly	tca Ser	gaa Glu	cag Gln	aag Lys	atc Ile	ccg Pro	gag Glu	gcc Ala	acc Thr	aac Asn	cgg Arg	cgt Arg	gtc Val 80	240
	tgg Trp	gaa Glu	ctg Leu	tcc Ser	aag Lys 85	gcc Ala	aat Asn	tcc Ser	cgc Arg	ttt Phe 90	gct Ala	acc Thr	act Thr	ttc Phe	tat Tyr 95	cag Gln	288
10	cac His	ctg Leu	gca Ala	gat Asp 100	tcc Ser	aag Lys	aat Asn	gac Asp	aat Asn 105	gat Asp	aac Asn	att Ile	ttc Phe	ctg Leu 110	tca Ser	ccc Pro	336
15	ctg Leu	agt Ser	atc Ile 115	tcc Ser	acg Thr	gct Ala	ttt Phe	gct Ala 120	atg Met	acc Thr	aag Lys	ctg Leu	ggt Gly 125	gcc Ala	tgt Cys	aat Asn	384
20	gac Asp 130	acc Thr	ctc Leu	cag Gln	caa Gln	ctg Leu	atg Met 135	gag Glu	gta Val	ttt Phe	aag Lys	ttt Phe 140	gac Asp	acc Thr	ata Ile	tct Ser	432
	gag Glu 145	aaa Lys	aca Thr	tct Ser	gat Asp 150	cag Gln	atc Ile	cac His	ttc Phe	ttc Phe	ttt Phe 155	gcc Ala	aaa Lys	ctg Leu	aac Asn	tgc Cys 160	480
25	cga Arg	ctc Leu	tat Tyr	cga Arg 165	aaa Lys	gcc Ala	aac Asn	aaa Lys	tcc Ser	tcc Ser 170	aag Lys	tta Leu	gta Val	tca Ser	gcc Ala 175	aat Asn	528
30	cgc Arg	ctt Leu	ttt Phe	gga Gly 180	gac Asp	aaa Lys	tcc Ser	ctt Leu	acc Thr 185	ttc Phe	aat Asn	gag Glu	acc Thr	tac Tyr 190	cag Gln	gac Asp	576
35	atc Ile	agt Ser	gag Glu 195	ttg Leu	gta Val	tat Tyr	gga Gly 200	gcc Ala	aag Lys	ctc Leu	cag Gln	ccc Pro	ctg Leu 205	gac Asp	ttc Phe	aag Lys	624
	gaa Glu 210	aat Asn	gca Ala	gag Glu	caa Gln	tcc Ser	aga Arg 215	gcg Ala	gcc Ala	atc Ile	aac Asn	aaa Lys 220	tgg Trp	gtg Val	tcc Ser	aat Asn	672
40	aag Lys 225	acc Thr	gaa Glu	ggc Gly	cga Arg	atc Ile 230	acc Thr	gat Asp	gtc Val	att Ile	ccc Pro 235	tcg Ser	gaa Glu	gcc Ala	atc Ile	aat Asn 240	720
45	gag Glu	ctc Leu	act Thr	gtt Val	ctg Leu 245	gtg Val	ctg Leu	gtt Val	aac Asn	acc Thr 250	att Ile	tac Tyr	ttc Phe	aag Lys	ggc Gly 255	ctg Leu	768
	tgg Trp	aag Lys	tca Ser	aag Lys 260	ttc Phe	agc Ser	cct Pro	gag Glu	aac Asn 265	aca Thr	agg Arg	aag Lys	gaa Glu	ctg Leu 270	ttc Phe	tac Tyr	816
50	aag Lys	gct Ala	gat Asp 275	gga Gly	gag Glu	tcg Ser	tgt Cys	tca Ser 280	gca Ala	tct Ser	atg Met	atg Met	tac Tyr 285	cag Gln	gaa Glu	ggc Gly	864
55	aag Lys	ttc Phe	cgt Arg	tat Tyr	cgg Arg	cgc Arg	gtg Val	gct Ala	gaa Glu	ggc Gly	acc Thr	cag Gln	gtg Val	ctt Leu	gag Glu	ttg Leu	912

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5	ccc ttc aaa ggt gat gac atc acc atg gtc ctc atc ttg ccc aag cct Pro Phe Lys Gly Asp Asp Ile Thr Met Val Leu Ile Leu Pro Lys Pro 305 310 315 320	960		
10	gag aag agc ctg gcc aag gta gag aag gaa ctc acc cca gag gtg ctg Glu Lys Ser Leu Ala Lys Val Glu Lys Glu Leu Thr Pro Glu Val Leu 325 330 335	1008		
15	caa gag tgg ctg gat gaa ttg gag gag atg atg ctg gtg gtc cac atg Gln Glu Trp Leu Asp Glu Leu Glu Glu Met Met Leu Val Val His Met 340 345 350	1056		
20	ccc cgc ttc cgc att gag gac ggc ttc agt ttg aag gag cag ctg caa Pro Arg Phe Arg Ile Glu Asp Gly Phe Ser Leu Lys Glu Gln Leu Gln 355 360 365	1104		
25	gac atg ggc ctt gtc gat ctg ttc agc cct gaa aag tcc aaa ctc cca Asp Met Gly Leu Val Asp Leu Phe Ser Pro Glu Lys Ser Lys Leu Pro 370 375 380	1152		
30	ggt att gtt gca gaa ggc cga gat gac ctc tat gtc tca gat gca ttc Gly Ile Val Ala Glu Gly Arg Asp Asp Leu Tyr Val Ser Asp Ala Phe 385 390 395 400	1200		
35	cat aag gca ttt ctt gag gta aat gaa gaa ggc agt gaa gca gct gca His Lys Ala Phe Leu Glu Val Asn Glu Glu Gly Ser Glu Ala Ala Ala 405 410 415	1248		
40	agt acc gct gtt gtg att gct ggc cta aac ccc aac agg gtg act ttc Ser Thr Ala Val Val Ile Ala Gly Leu Asn Pro Asn Arg Val Thr Phe 420 425 430	1296		
45	aag gcc aac agg cct ttc ctg gtt ttt ata aga gaa gtt cct ctg aac Lys Ala Asn Arg Pro Phe Leu Val Phe Ile Arg Glu Val Pro Leu Asn 435 440 445	1344		
50	act att atc ttc atg ggc aga gta gcc aac cct tgt gtt aag Thr Ile Ile Phe Met Gly Arg Val Ala Asn Pro Cys Val Lys 450 455 460	1386		
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5	Tyr	Leu	Leu	Ser	Leu	Leu	Leu	Ile	Gly	Phe	Trp	Asp	Cys	Val	Thr	Cys
				20					25					30		

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	His	Gly	Ser	Pro	Val	Asp	Ile	Cys	Thr	Ala	Lys	Pro	Arg	Asp	Ile	Pro	
			35					40					45				
5	Met	Asn	Pro	Met	Cys	Ile	Tyr	Arg	Ser	Pro	Glu	Lys	Lys	Ala	Thr	Glu	
		50					55					60					
10	Asp	Glu	Gly	Ser	Glu	Gln	Lys	Ile	Pro	Glu	Ala	Thr	Asn	Arg	Arg	Val	
	65					70					75					80	
15	Trp	Glu	Leu	Ser	Lys	Ala	Asn	Ser	Arg	Phe	Ala	Thr	Thr	Phe	Tyr	Gln	
					85					90					95		
20	His	Leu	Ala	Asp	Ser	Lys	Asn	Asp	Asn	Asp	Asn	Ile	Phe	Leu	Ser	Pro	
				100					105					110			
25	Leu	Ser	Ile	Ser	Thr	Ala	Phe	Ala	Met	Thr	Lys	Leu	Gly	Ala	Cys	Asn	
			115					120					125				
30	Asp	Thr	Leu	Gln	Gln	Leu	Met	Glu	Val	Phe	Lys	Phe	Asp	Thr	Ile	Ser	
		130					135					140					
35	Glu	Lys	Thr	Ser	Asp	Gln	Ile	His	Phe	Phe	Phe	Ala	Lys	Leu	Asn	Cys	
	145					150					155					160	
40	Arg	Leu	Tyr	Arg	Lys	Ala	Asn	Lys	Ser	Ser	Lys	Leu	Val	Ser	Ala	Asn	
					165					170					175		
45	Arg	Leu	Phe	Gly	Asp	Lys	Ser	Leu	Thr	Phe	Asn	Glu	Thr	Tyr	Gln	Asp	
				180					185					190			
50	Ile	Ser	Glu	Leu	Val	Tyr	Gly	Ala	Lys	Leu	Gln	Pro	Leu	Asp	Phe	Lys	
			195					200					205				
55	Glu	Asn	Ala	Glu	Gln	Ser	Arg	Ala	Ala	Ile	Asn	Lys	Trp	Val	Ser	Asn	
		210					215					220					
60	Lys	Thr	Glu	Gly	Arg	Ile	Thr	Asp	Val	Ile	Pro	Ser	Glu	Ala	Ile	Asn	
	225					230					235					240	
65	Glu	Leu	Thr	Val	Leu	Val	Leu	Val	Asn	Thr	Ile	Tyr	Phe	Lys	Gly	Leu	
					245					250					255		
70	Trp	Lys	Ser	Lys	Phe	Ser	Pro	Glu	Asn	Thr	Arg	Lys	Glu	Leu	Phe	Tyr	
				260					265					270			

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Lys Ala Asp Gly Glu Ser Cys Ser Ala Ser Met Met Tyr Gln Glu Gly
275 280 285

5 Lys Phe Arg Tyr Arg Arg Val Ala Glu Gly Thr Gln Val Leu Glu Leu
290 295 300

10 Pro Phe Lys Gly Asp Asp Ile Thr Met Val Leu Ile Leu Pro Lys Pro
305 310 315 320

15 Glu Lys Ser Leu Ala Lys Val Glu Lys Glu Leu Thr Pro Glu Val Leu
325 330 335

20 Gln Glu Trp Leu Asp Glu Leu Glu Glu Met Met Leu Val Val His Met
340 345 350

25 Pro Arg Phe Arg Ile Glu Asp Gly Phe Ser Leu Lys Glu Gln Leu Gln
355 360 365

30 Asp Met Gly Leu Val Asp Leu Phe Ser Pro Glu Lys Ser Lys Leu Pro
370 375 380

35 Gly Ile Val Ala Glu Gly Arg Asp Asp Leu Tyr Val Ser Asp Ala Phe
385 390 395 400

His Lys Ala Phe Leu Glu Val Asn Glu Glu Gly Ser Glu Ala Ala Ala
405 410 415

40 Ser Thr Ala Val Val Ile Ala Gly Leu Asn Pro Asn Arg Val Thr Phe
420 425 430

45 Lys Ala Asn Arg Pro Phe Leu Val Phe Ile Arg Glu Val Pro Leu Asn
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50 Thr Ile Ile Phe Met Gly Arg Val Ala Asn Pro Cys Val Lys
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	Tyr	Leu	Leu	Ser	Leu	Leu	Leu	Ile	Gly	Phe	Trp	Asp	Cys	Val	Thr	Cys	
				20					25					30			
10	cac	ggg	agc	cct	gtg	gac	atc	tgc	aca	gcc	aag	ccg	cgg	gac	att	ccc	144
	His	Gly	Ser	Pro	Val	Asp	Ile	Cys	Thr	Ala	Lys	Pro	Arg	Asp	Ile	Pro	
			35					40					45				
15	atg	aat	ccc	atg	tgc	att	tac	cgc	tcc	ccg	gag	aag	aag	gca	act	gag	192
	Met	Asn	Pro	Met	Cys	Ile	Tyr	Arg	Ser	Pro	Glu	Lys	Lys	Ala	Thr	Glu	
		50				55					60						
20	gat	gag	ggc	tca	gaa	cag	aag	atc	ccg	gag	gcc	acc	aac	cgg	cgt	gtc	240
	Asp	Glu	Gly	Ser	Glu	Gln	Lys	Ile	Pro	Glu	Ala	Thr	Asn	Arg	Arg	Val	
	65				70					75					80		
25	tgg	gaa	ctg	tcc	aag	gcc	aat	tcc	cgc	ttt	gct	acc	act	ttc	tat	cag	288
	Trp	Glu	Leu	Ser	Lys	Ala	Asn	Ser	Arg	Phe	Ala	Thr	Thr	Phe	Tyr	Gln	
				85					90					95			
30	cac	ctg	gca	gat	tcc	aag	aat	gac	aat	gat	aac	att	ttc	ctg	tca	ccc	336
	His	Leu	Ala	Asp	Ser	Lys	Asn	Asp	Asn	Asp	Asn	Ile	Phe	Leu	Ser	Pro	
			100					105					110				
35	ctg	agt	atc	tcc	acg	gct	ttt	gct	atg	acc	aag	ctg	ggt	gcc	tgt	aat	384
	Leu	Ser	Ile	Ser	Thr	Ala	Phe	Ala	Met	Thr	Lys	Leu	Gly	Ala	Cys	Asn	
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	Arg	Leu	Tyr	Arg	Lys	Ala	Gln	Lys	Ser	Ser	Lys	Leu	Val	Ser	Ala	Asn	
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	Arg	Leu	Phe	Gly	Asp	Lys	Ser	Leu	Thr	Phe	Asn	Glu	Thr	Tyr	Gln	Asp	
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	Ile	Ser	Glu	Leu	Val	Tyr	Gly	Ala	Lys	Leu	Gln	Pro	Leu	Asp	Phe	Lys	
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	Trp	Lys	Ser	Lys	Phe	Ser	Pro	Glu	Asn	Thr	Arg	Lys	Glu	Leu	Phe	Tyr	
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	Lys	Phe	Arg	Tyr	Arg	Arg	Val	Ala	Glu	Gly	Thr	Gln	Val	Leu	Glu	Leu	
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	Ser	Thr	Ala	Val	Val	Ile	Ala	Gly	Ser	Leu	Asn	Pro	Asn	Arg	Val	Thr	
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	Phe	Lys	Ala	Asn	Arg	Pro	Phe	Leu	Val	Phe	Ile	Arg	Glu	Val	Pro	Leu	
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 His Gly Ser Pro Val Asp Ile Cys Thr Ala Lys Pro Arg Asp Ile Pro
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35 atg aat ccc atg tgc att tac cgc tcc ccg gag aag aag gca act gag 192
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40 gat gag ggc tca gaa cag aag atc ccg gag gcc acc aac cgg cgt gtc 240
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 85 90 95

50 cac ctg gca gat tcc aag aat gac aat gat aac att ttc ctg tca ccc 336
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 100 105 110

55 ctg agt atc tcc acg gct ttt gct atg acc aag ctg ggt gcc tgt aat 384
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 115 120 125

60 gac acc ctc cag caa ctg atg gag gta ttt aag ttt gac acc ata tct 432
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 130 135 140

65 gag aaa aca tct gat cag atc cac ttc ttc ttt gcc aaa ctg aac tgc 480
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	Trp	Lys	Ser	Lys	Phe	Ser	Pro	Glu	Asn	Thr	Arg	Lys	Glu	Leu	Phe	Tyr	
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	Lys	Ala	Asp	Gly	Glu	Ser	Cys	Ser	Ala	Ser	Met	Met	Tyr	Gln	Glu	Gly	
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					405					410					415		

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5	ttc aag gcc aac agg cct ttc ctg gtt ttt ata aga gaa gtt cct ctg	1344
	Phe Lys Ala Asn Arg Pro Phe Leu Val Phe Ile Arg Glu Val Pro Leu	
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10	aac act att atc ttc atg ggc aga gta gcc aac cct tgt gtt aag	1389
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Leu	Ser	Ile	Ser	Thr	Ala	Phe	Ala	Met	Thr	Lys	Leu	Gly	Ala	Cys	Asn
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	Pro	Arg	Phe	Arg	Ile	Glu	Asp	Gly	Phe	Ser	Leu	Lys	Glu	Gln	Leu	Gln		355	360							365		
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5 His Lys Ala Phe Leu Glu Val Asn Glu Glu Gly Ser Glu Ala Ala Ala
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10 Ser Thr Ala Val Val Ile Ala Gly Arg Leu Asn Pro Asn Arg Val Thr
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	Asp	Glu	Gly	Ser	Glu	Gln	Lys	Ile	Pro	Glu	Ala	Thr	Asn	Arg	Arg	Val	
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	Trp	Glu	Leu	Ser	Lys	Ala	Asn	Ser	Arg	Phe	Ala	Thr	Thr	Phe	Tyr	Gln	
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30	cac	ctg	gca	gat	tcc	aag	aat	gac	aat	gat	aac	att	ttc	ctg	tca	ccc	336
	His	Leu	Ala	Asp	Ser	Lys	Asn	Asp	Asn	Asp	Asn	Ile	Phe	Leu	Ser	Pro	
				100					105					110			
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	Asp	Thr	Leu	Gln	Gln	Leu	Met	Glu	Val	Phe	Lys	Phe	Asp	Thr	Ile	Ser	
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	Glu	Lys	Thr	Ser	Asp	Gln	Ile	His	Phe	Phe	Phe	Ala	Lys	Leu	Asn	Cys	
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	Arg	Leu	Tyr	Arg	Lys	Ala	Gln	Lys	Ser	Ser	Lys	Leu	Val	Ser	Ala	Asn	
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	Arg	Leu	Phe	Gly	Asp	Lys	Ser	Leu	Thr	Phe	Asn	Glu	Thr	Tyr	Gln	Asp	
				180					185					190			
25	atc	agt	gag	ttg	gta	tat	gga	gcc	aag	ctc	cag	ccc	ctg	gac	ttc	aag	624
	Ile	Ser	Glu	Leu	Val	Tyr	Gly	Ala	Lys	Leu	Gln	Pro	Leu	Asp	Phe	Lys	
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	Glu	Asn	Ala	Glu	Gln	Ser	Arg	Ala	Ala	Ile	Asn	Lys	Trp	Val	Ser	Asn	
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	Lys	Thr	Glu	Gly	Arg	Ile	Thr	Asp	Val	Ile	Pro	Ser	Glu	Ala	Ile	Asn	
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40	gag	ctc	act	gtt	ctg	gtg	ctg	gtt	aac	acc	att	tac	ttc	aag	ggc	ctg	768
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	Trp	Lys	Ser	Lys	Phe	Ser	Pro	Glu	Asn	Thr	Arg	Lys	Glu	Leu	Phe	Tyr	
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	Lys	Ala	Asp	Gly	Glu	Ser	Cys	Ser	Ala	Ser	Met	Met	Tyr	Gln	Glu	Gly	
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	Pro	Phe	Lys	Gly	Asp	Asp	Ile	Thr	Met	Val	Leu	Ile	Leu	Pro	Lys	Pro	
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65	gag	aag	agc	ctg	gcc	aag	gta	gag	aag	gaa	ctc	acc	cca	gag	gtg	ctg	1008
	Glu	Lys	Ser	Leu	Ala	Lys	Val	Glu	Lys	Glu	Leu	Thr	Pro	Glu	Val	Leu	
					325					330					335		
70	caa	gag	tgg	ctg	gat	gaa	ttg	gag	gag	atg	atg	ctg	gtg	gtc	cac	atg	1056
	Gln	Glu	Trp	Leu	Asp	Glu	Leu	Glu	Glu	Met	Met	Leu	Val	Val	His	Met	
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75	ccc	cgc	ttc	cgc	att	gag	gac	ggc	ttc	agt	ttg	aag	gag	cag	ctg	caa	1104

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	Pro	Arg	Phe	Arg	Ile	Glu	Asp	Gly	Phe	Ser	Leu	Lys	Glu	Gln	Leu	Gln	
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	Gly	Ile	Val	Ala	Glu	Gly	Arg	Asp	Asp	Leu	Tyr	Val	Ser	Asp	Ala	Phe	
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15	cat	aag	gca	ttt	ctt	gag	gta	aat	gaa	gaa	ggc	agt	gaa	gca	gct	gca	1248
	His	Lys	Ala	Phe	Leu	Glu	Val	Asn	Glu	Glu	Gly	Ser	Glu	Ala	Ala	Ala	
					405					410					415		
20	agt	acc	gct	gtt	gtg	att	gct	ggc	cta	aac	ccc	aac	agg	gtg	act	ttc	1296
	Ser	Thr	Ala	Val	Val	Ile	Ala	Gly	Leu	Asn	Pro	Asn	Arg	Val	Thr	Phe	
				420					425					430			
25	aag	gcc	aac	agg	cct	ttc	ctg	gtt	ttt	ata	aga	gaa	gtt	cct	ctg	aac	1344
	Lys	Ala	Asn	Arg	Pro	Phe	Leu	Val	Phe	Ile	Arg	Glu	Val	Pro	Leu	Asn	
			435					440					445				
30	act	att	atc	ttc	atg	ggc	aga	gta	gcc	aac	cct	tgt	gtt	aag			1386
	Thr	Ile	Ile	Phe	Met	Gly	Arg	Val	Ala	Asn	Pro	Cys	Val	Lys			
		450					455					460					
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5 Tyr Leu Leu Ser Leu Leu Leu Ile Gly Phe Trp Asp Cys Val Thr Cys
20 25 30

10 His Gly Ser Pro Val Asp Ile Cys Thr Ala Lys Pro Arg Asp Ile Pro
35 40 45

15 Met Asn Pro Met Cys Ile Tyr Arg Ser Pro Glu Lys Lys Ala Thr Glu
50 55 60

20 Asp Glu Gly Ser Glu Gln Lys Ile Pro Glu Ala Thr Asn Arg Arg Val
65 70 75 80

25 Trp Glu Leu Ser Lys Ala Asn Ser Arg Phe Ala Thr Thr Phe Tyr Gln

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	85					90					95					
5	His	Leu	Ala	Asp	Ser	Lys	Asn	Asp	Asn	Asp	Asn	Ile	Phe	Leu	Ser	Pro
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10	Leu	Ser	Ile	Ser	Thr	Ala	Phe	Ala	Met	Thr	Lys	Leu	Gly	Ala	Cys	Asn
			115					120					125			
15	Asp	Thr	Leu	Gln	Gln	Leu	Met	Glu	Val	Phe	Lys	Phe	Asp	Thr	Ile	Ser
		130					135						140			
20	Glu	Lys	Thr	Ser	Asp	Gln	Ile	His	Phe	Phe	Phe	Ala	Lys	Leu	Asn	Cys
	145					150					155					160
25	Arg	Leu	Tyr	Arg	Lys	Ala	Gln	Lys	Ser	Ser	Lys	Leu	Val	Ser	Ala	Asn
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30	Arg	Leu	Phe	Gly	Asp	Lys	Ser	Leu	Thr	Phe	Asn	Glu	Thr	Tyr	Gln	Asp
				180					185					190		
35	Ile	Ser	Glu	Leu	Val	Tyr	Gly	Ala	Lys	Leu	Gln	Pro	Leu	Asp	Phe	Lys
			195					200					205			
40	Glu	Asn	Ala	Glu	Gln	Ser	Arg	Ala	Ala	Ile	Asn	Lys	Trp	Val	Ser	Asn
		210					215					220				
45	Lys	Thr	Glu	Gly	Arg	Ile	Thr	Asp	Val	Ile	Pro	Ser	Glu	Ala	Ile	Asn
	225					230					235					240
50	Glu	Leu	Thr	Val	Leu	Val	Leu	Val	Asn	Thr	Ile	Tyr	Phe	Lys	Gly	Leu
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55	Trp	Lys	Ser	Lys	Phe	Ser	Pro	Glu	Asn	Thr	Arg	Lys	Glu	Leu	Phe	Tyr
				260					265					270		
60	Lys	Ala	Asp	Gly	Glu	Ser	Cys	Ser	Ala	Ser	Met	Met	Tyr	Gln	Glu	Gly
			275					280					285			
65	Lys	Phe	Arg	Tyr	Arg	Arg	Val	Ala	Glu	Gly	Thr	Gln	Val	Leu	Glu	Leu
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75	Glu	Lys	Ser	Leu	Ala	Lys	Val	Glu	Lys	Glu	Leu	Thr	Pro	Glu	Val	Leu

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5 Gln Glu Trp Leu Asp Glu Leu Glu Glu Met Met Leu Val Val His Met
340 345 350

10 Pro Arg Phe Arg Ile Glu Asp Gly Phe Ser Leu Lys Glu Gln Leu Gln
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15 Asp Met Gly Leu Val Asp Leu Phe Ser Pro Glu Lys Ser Lys Leu Pro
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20 Gly Ile Val Ala Glu Gly Arg Asp Asp Leu Tyr Val Ser Asp Ala Phe
385 390 395 400

25 His Lys Ala Phe Leu Glu Val Asn Glu Glu Gly Ser Glu Ala Ala Ala
405 410 415

30 Ser Thr Ala Val Val Ile Ala Gly Leu Asn Pro Asn Arg Val Thr Phe
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35 Lys Ala Asn Arg Pro Phe Leu Val Phe Ile Arg Glu Val Pro Leu Asn
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	atg aat ccc atg tgc att tac cgc tcc ccg gag aag aag gca act gag	96
	Met Asn Pro Met Cys Ile Tyr Arg Ser Pro Glu Lys Lys Ala Thr Glu	
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15	gat gag ggc tca gaa cag aag atc ccg gag gcc acc aac cgg cgt gtc	144
	Asp Glu Gly Ser Glu Gln Lys Ile Pro Glu Ala Thr Asn Arg Arg Val	
	35 40 45	
20	tgg gaa ctg tcc aag gcc aat tcc cgc ttt gct acc act ttc tat cag	192
	Trp Glu Leu Ser Lys Ala Asn Ser Arg Phe Ala Thr Thr Phe Tyr Gln	
	50 55 60	
25	cac ctg gca gat tcc aag aat gac aat gat aac att ttc ctg tca ccc	240
	His Leu Ala Asp Ser Lys Asn Asp Asn Asp Asn Ile Phe Leu Ser Pro	
	65 70 75 80	
30	ctg agt atc tcc acg gct ttt gct atg acc aag ctg ggt gcc tgt aat	288
	Leu Ser Ile Ser Thr Ala Phe Ala Met Thr Lys Leu Gly Ala Cys Asn	
	85 90 95	
35	gac acc ctc cag caa ctg atg gag gta ttt aag ttt gac acc ata tct	336
	Asp Thr Leu Gln Gln Leu Met Glu Val Phe Lys Phe Asp Thr Ile Ser	
	100 105 110	
40	gag aaa aca tct gat cag atc cac ttc ttc ttt gcc aaa ctg aac tgc	384
	Glu Lys Thr Ser Asp Gln Ile His Phe Phe Phe Ala Lys Leu Asn Cys	
	115 120 125	
45	cga ctc tat cga aaa gcc aac aaa tcc tcc aag tta gta tca gcc aat	432
	Arg Leu Tyr Arg Lys Ala Asn Lys Ser Ser Lys Leu Val Ser Ala Asn	
	130 135 140	
50	cgc ctt ttt gga gac aaa tcc ctt acc ttc aat gag acc tac cag gac	480
	Arg Leu Phe Gly Asp Lys Ser Leu Thr Phe Asn Glu Thr Tyr Gln Asp	
	145 150 155 160	
55	atc agt gag ttg gta tat gga gcc aag ctc cag ccc ctg gac ttc aag	528
	Ile Ser Glu Leu Val Tyr Gly Ala Lys Leu Gln Pro Leu Asp Phe Lys	
	165 170 175	
60	gaa aat gca gag caa tcc aga gcg gcc atc aac aaa tgg gtg tcc aat	576
	Glu Asn Ala Glu Gln Ser Arg Ala Ala Ile Asn Lys Trp Val Ser Asn	
	180 185 190	
65	aag acc gaa ggc cga atc acc gat gtc att ccc tcg gaa gcc atc aat	624
	Lys Thr Glu Gly Arg Ile Thr Asp Val Ile Pro Ser Glu Ala Ile Asn	

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10	tgg	aag	tca	aag	ttc	agc	cct	gag	aac	aca	agg	aag	gaa	ctg	ttc	tac	720
	Trp	Lys	Ser	Lys	Phe	Ser	Pro	Glu	Asn	Thr	Arg	Lys	Glu	Leu	Phe	Tyr	
	225					230					235					240	
15	aag	gct	gat	gga	gag	tcg	tgt	tca	gca	tct	atg	atg	tac	cag	gaa	ggc	768
	Lys	Ala	Asp	Gly	Glu	Ser	Cys	Ser	Ala	Ser	Met	Met	Tyr	Gln	Glu	Gly	
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20	aag	ttc	cgt	tat	cgg	cgc	gtg	gct	gaa	ggc	acc	cag	gtg	ctt	gag	ttg	816
	Lys	Phe	Arg	Tyr	Arg	Arg	Val	Ala	Glu	Gly	Thr	Gln	Val	Leu	Glu	Leu	
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25	ccc	ttc	aaa	ggt	gat	gac	atc	acc	atg	gtc	ctc	atc	ttg	ccc	aag	cct	864
	Pro	Phe	Lys	Gly	Asp	Asp	Ile	Thr	Met	Val	Leu	Ile	Leu	Pro	Lys	Pro	
	275					280					285						
30	gag	aag	agc	ctg	gcc	aag	gtg	gag	aag	gaa	ctc	acc	cca	gag	gtg	ctg	912
	Glu	Lys	Ser	Leu	Ala	Lys	Val	Glu	Lys	Glu	Leu	Thr	Pro	Glu	Val	Leu	
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	Gln	Glu	Trp	Leu	Asp	Glu	Leu	Glu	Glu	Met	Met	Leu	Val	Val	His	Met	
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	Asp	Met	Gly	Leu	Val	Asp	Leu	Phe	Ser	Pro	Glu	Lys	Ser	Lys	Leu	Pro	
	340					345					350						
50	ggt	att	gtt	gca	gaa	ggc	cga	gat	gac	ctc	tat	gtc	tca	gat	gca	ttc	1104
	Gly	Ile	Val	Ala	Glu	Gly	Arg	Asp	Asp	Leu	Tyr	Val	Ser	Asp	Ala	Phe	
	355					360					365						
55	cat	aag	gca	ttt	ctt	gag	gta	aat	gaa	gaa	ggc	agt	gaa	gca	gct	gca	1152
	His	Lys	Ala	Phe	Leu	Glu	Val	Asn	Glu	Glu	Gly	Ser	Glu	Ala	Ala	Ala	
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	Thr	Phe	Lys	Ala	Asn	Arg	Pro	Phe	Leu	Val	Phe	Ile	Arg	Glu	Val	Pro	
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				20					25					30			
10	Asp	Glu	Gly	Ser	Glu	Gln	Lys	Ile	Pro	Glu	Ala	Thr	Asn	Arg	Arg	Val	
			35					40					45				
15	Trp	Glu	Leu	Ser	Lys	Ala	Asn	Ser	Arg	Phe	Ala	Thr	Thr	Phe	Tyr	Gln	
	50						55					60					
20	His	Leu	Ala	Asp	Ser	Lys	Asn	Asp	Asn	Asp	Asn	Ile	Phe	Leu	Ser	Pro	
	65					70					75					80	
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					85					90					95		
30	Asp	Thr	Leu	Gln	Gln	Leu	Met	Glu	Val	Phe	Lys	Phe	Asp	Thr	Ile	Ser	
				100					105					110			
35	Glu	Lys	Thr	Ser	Asp	Gln	Ile	His	Phe	Phe	Phe	Ala	Lys	Leu	Asn	Cys	
			115					120					125				
40	Arg	Leu	Tyr	Arg	Lys	Ala	Asn	Lys	Ser	Ser	Lys	Leu	Val	Ser	Ala	Asn	
	130						135					140					
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	145					150					155					160	
50	Ile	Ser	Glu	Leu	Val	Tyr	Gly	Ala	Lys	Leu	Gln	Pro	Leu	Asp	Phe	Lys	
					165					170					175		
55	Glu	Asn	Ala	Glu	Gln	Ser	Arg	Ala	Ala	Ile	Asn	Lys	Trp	Val	Ser	Asn	
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60	Lys	Thr	Glu	Gly	Arg	Ile	Thr	Asp	Val	Ile	Pro	Ser	Glu	Ala	Ile	Asn	
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	225					230					235					240
10	Lys	Ala	Asp	Gly	Glu	Ser	Cys	Ser	Ala	Ser	Met	Met	Tyr	Gln	Glu	Gly
					245					250					255	
15	Lys	Phe	Arg	Tyr	Arg	Arg	Val	Ala	Glu	Gly	Thr	Gln	Val	Leu	Glu	Leu
				260					265					270		
20	Pro	Phe	Lys	Gly	Asp	Asp	Ile	Thr	Met	Val	Leu	Ile	Leu	Pro	Lys	Pro
			275					280					285			
25	Glu	Lys	Ser	Leu	Ala	Lys	Val	Glu	Lys	Glu	Leu	Thr	Pro	Glu	Val	Leu
	290						295					300				
30	Gln	Glu	Trp	Leu	Asp	Glu	Leu	Glu	Glu	Met	Met	Leu	Val	Val	His	Met
	305					310					315					320
35	Pro	Arg	Phe	Arg	Ile	Glu	Asp	Gly	Phe	Ser	Leu	Lys	Glu	Gln	Leu	Gln
					325					330					335	
40	Asp	Met	Gly	Leu	Val	Asp	Leu	Phe	Ser	Pro	Glu	Lys	Ser	Lys	Leu	Pro
				340					345					350		
45	Gly	Ile	Val	Ala	Glu	Gly	Arg	Asp	Asp	Leu	Tyr	Val	Ser	Asp	Ala	Phe
			355					360					365			
50	His	Lys	Ala	Phe	Leu	Glu	Val	Asn	Glu	Glu	Gly	Ser	Glu	Ala	Ala	Ala
	370						375					380				
55	Ser	Thr	Ala	Val	Val	Ile	Ala	Gly	Arg	Gln	Leu	Asn	Pro	Asn	Arg	Val
	385					390					395					400
60	Thr	Phe	Lys	Ala	Asn	Arg	Pro	Phe	Leu	Val	Phe	Ile	Arg	Glu	Val	Pro
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5	atg	aat	ccc	atg	tgc	att	tac	cgc	tcc	ccg	gag	aag	aag	gca	act	gag	96
	Met	Asn	Pro	Met	Cys	Ile	Tyr	Arg	Ser	Pro	Glu	Lys	Lys	Ala	Thr	Glu	
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10	gat	gag	ggc	tca	gaa	cag	aag	atc	ccg	gag	gcc	acc	aac	cgg	cgt	gtc	144
	Asp	Glu	Gly	Ser	Glu	Gln	Lys	Ile	Pro	Glu	Ala	Thr	Asn	Arg	Arg	Val	
			35					40					45				
15	tgg	gaa	ctg	tcc	aag	gcc	aat	tcc	cgc	ttt	gct	acc	act	ttc	tat	cag	192
	Trp	Glu	Leu	Ser	Lys	Ala	Asn	Ser	Arg	Phe	Ala	Thr	Thr	Phe	Tyr	Gln	
		50					55					60					
20	cac	ctg	gca	gat	tcc	aag	aat	gac	aat	gat	aac	att	ttc	ctg	tca	ccc	240
	His	Leu	Ala	Asp	Ser	Lys	Asn	Asp	Asn	Asp	Asn	Ile	Phe	Leu	Ser	Pro	
	65					70					75					80	
25	ctg	agt	atc	tcc	acg	gct	ttt	gct	atg	acc	aag	ctg	ggt	gcc	tgt	aat	288
	Leu	Ser	Ile	Ser	Thr	Ala	Phe	Ala	Met	Thr	Lys	Leu	Gly	Ala	Cys	Asn	
					85					90					95		
30	gac	acc	ctc	cag	caa	ctg	atg	gag	gta	ttt	aag	ttt	gac	acc	ata	tct	336
	Asp	Thr	Leu	Gln	Gln	Leu	Met	Glu	Val	Phe	Lys	Phe	Asp	Thr	Ile	Ser	
				100					105					110			
35	gag	aaa	aca	tct	gat	cag	atc	cac	ttc	ttc	ttt	gcc	aaa	ctg	aac	tgc	384
	Glu	Lys	Thr	Ser	Asp	Gln	Ile	His	Phe	Phe	Phe	Ala	Lys	Leu	Asn	Cys	
			115					120					125				
40	cga	ctc	tat	cga	aaa	gcc	aac	aaa	tcc	tcc	aag	tta	gta	tca	gcc	aat	432
	Arg	Leu	Tyr	Arg	Lys	Ala	Asn	Lys	Ser	Ser	Lys	Leu	Val	Ser	Ala	Asn	
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	145				150						155					160	
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	Ile	Ser	Glu	Leu	Val	Tyr	Gly	Ala	Lys	Leu	Gln	Pro	Leu	Asp	Phe	Lys	
					165					170					175		
55	gaa	aat	gca	gag	caa	tcc	aga	gcg	gcc	atc	aac	aaa	tgg	gtg	tcc	aat	576
	Glu	Asn	Ala	Glu	Gln	Ser	Arg	Ala	Ala	Ile	Asn	Lys	Trp	Val	Ser	Asn	
				180					185					190			
60	aag	acc	gaa	ggc	cga	atc	acc	gat	gtc	att	ccc	tcg	gaa	gcc	atc	aat	624
	Lys	Thr	Glu	Gly	Arg	Ile	Thr	Asp	Val	Ile	Pro	Ser	Glu	Ala	Ile	Asn	
			195					200					205				
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[illegible]

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5	Met	Asn	Pro	Met	Cys	Ile	Tyr	Arg	Ser	Pro	Glu	Lys	Lys	Ala	Thr	Glu
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10	Asp	Glu	Gly	Ser	Glu	Gln	Lys	Ile	Pro	Glu	Ala	Thr	Asn	Arg	Arg	Val
			35					40					45			
15	Trp	Glu	Leu	Ser	Lys	Ala	Asn	Ser	Arg	Phe	Ala	Thr	Thr	Phe	Tyr	Gln
	50						55					60				
20	His	Leu	Ala	Asp	Ser	Lys	Asn	Asp	Asn	Asp	Asn	Ile	Phe	Leu	Ser	Pro
	65					70					75					80
25	Leu	Ser	Ile	Ser	Thr	Ala	Phe	Ala	Met	Thr	Lys	Leu	Gly	Ala	Cys	Asn
					85					90					95	
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35	Glu	Lys	Thr	Ser	Asp	Gln	Ile	His	Phe	Phe	Phe	Ala	Lys	Leu	Asn	Cys
			115					120					125			
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		130					135					140				
45	Arg	Leu	Phe	Gly	Asp	Lys	Ser	Leu	Thr	Phe	Asn	Glu	Thr	Tyr	Gln	Asp
	145					150					155					160
50	Ile	Ser	Glu	Leu	Val	Tyr	Gly	Ala	Lys	Leu	Gln	Pro	Leu	Asp	Phe	Lys
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				180					185					190		
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5	Lys	Ala	Asp	Gly	Glu	Ser	Cys	Ser	Ala	Ser	Met	Met	Tyr	Gln	Glu	Gly
					245					250					255	
10	Lys	Phe	Arg	Tyr	Arg	Arg	Val	Ala	Glu	Gly	Thr	Gln	Val	Leu	Glu	Leu
				260					265					270		
15	Pro	Phe	Lys	Gly	Asp	Asp	Ile	Thr	Met	Val	Leu	Ile	Leu	Pro	Lys	Pro
			275					280					285			
20	Glu	Lys	Ser	Leu	Ala	Lys	Val	Glu	Lys	Glu	Leu	Thr	Pro	Glu	Val	Leu
		290					295					300				
25	Gln	Glu	Trp	Leu	Asp	Glu	Leu	Glu	Glu	Met	Met	Leu	Val	Val	His	Met
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30	Pro	Arg	Phe	Arg	Ile	Glu	Asp	Gly	Phe	Ser	Leu	Lys	Glu	Gln	Leu	Gln
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35	Asp	Met	Gly	Leu	Val	Asp	Leu	Phe	Ser	Pro	Glu	Lys	Ser	Lys	Leu	Pro
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40	Gly	Ile	Val	Ala	Glu	Gly	Arg	Asp	Asp	Leu	Tyr	Val	Ser	Asp	Ala	Phe
			355					360					365			
45	His	Lys	Ala	Phe	Leu	Glu	Val	Asn	Glu	Glu	Gly	Ser	Glu	Ala	Ala	Ala
		370					375					380				
50	Ser	Thr	Ala	Val	Val	Ile	Ala	Gly	Arg	Glu	Leu	Asn	Pro	Asn	Arg	Val
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55	Thr	Phe	Lys	Ala	Asn	Arg	Pro	Phe	Leu	Val	Phe	Ile	Arg	Glu	Val	Pro
					405					410					415	
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5	atg	aat	ccc	atg	tgc	att	tac	cgc	tcc	ccg	gag	aag	aag	gca	act	gag	96
	Met	Asn	Pro	Met	Cys	Ile	Tyr	Arg	Ser	Pro	Glu	Lys	Lys	Ala	Thr	Glu	
				20					25					30			
10	gat	gag	ggc	tca	gaa	cag	aag	atc	ccg	gag	gcc	acc	aac	cgg	cgt	gtc	144
	Asp	Glu	Gly	Ser	Glu	Gln	Lys	Ile	Pro	Glu	Ala	Thr	Asn	Arg	Arg	Val	
			35					40					45				
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	Trp	Glu	Leu	Ser	Lys	Ala	Asn	Ser	Arg	Phe	Ala	Thr	Thr	Phe	Tyr	Gln	
		50					55					60					
20	cac	ctg	gca	gat	tcc	aag	aat	gac	aat	gat	aac	att	ttc	ctg	tca	ccc	240
	His	Leu	Ala	Asp	Ser	Lys	Asn	Asp	Asn	Asp	Asn	Ile	Phe	Leu	Ser	Pro	
	65					70					75					80	
25	ctg	agt	atc	tcc	acg	gct	ttt	gct	atg	acc	aag	ctg	ggg	gcc	tgt	aat	288
	Leu	Ser	Ile	Ser	Thr	Ala	Phe	Ala	Met	Thr	Lys	Leu	Gly	Ala	Cys	Asn	
					85					90					95		
30	gac	acc	ctc	cag	caa	ctg	atg	gag	gta	ttt	aag	ttt	gac	acc	ata	tct	336
	Asp	Thr	Leu	Gln	Gln	Leu	Met	Glu	Val	Phe	Lys	Phe	Asp	Thr	Ile	Ser	
				100					105					110			
35	gag	aaa	aca	tct	gat	cag	atc	cac	ttc	ttc	ttt	gcc	aaa	ctg	aac	tgc	384
	Glu	Lys	Thr	Ser	Asp	Gln	Ile	His	Phe	Phe	Phe	Ala	Lys	Leu	Asn	Cys	
			115				120						125				
40	cga	ctc	tat	cga	aaa	gcc	cag	aaa	tcc	tcc	aag	tta	gta	tca	gcc	aat	432
	Arg	Leu	Tyr	Arg	Lys	Ala	Gln	Lys	Ser	Ser	Lys	Leu	Val	Ser	Ala	Asn	
		130					135					140					
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	Arg	Leu	Phe	Gly	Asp	Lys	Ser	Leu	Thr	Phe	Asn	Glu	Thr	Tyr	Gln	Asp	
	145					150					155					160	
50	atc	agt	gag	ttg	gta	tat	gga	gcc	aag	ctc	cag	ccc	ctg	gac	ttc	aag	528
	Ile	Ser	Glu	Leu	Val	Tyr	Gly	Ala	Lys	Leu	Gln	Pro	Leu	Asp	Phe	Lys	
					165					170					175		
55	gaa	aat	gca	gag	caa	tcc	aga	gcg	gcc	atc	aac	aaa	tgg	gtg	tcc	aat	576
	Glu	Asn	Ala	Glu	Gln	Ser	Arg	Ala	Ala	Ile	Asn	Lys	Trp	Val	Ser	Asn	
				180					185					190			
60	aag	acc	gaa	ggc	cga	atc	acc	gat	gtc	att	ccc	tcg	gaa	gcc	atc	aat	624
	Lys	Thr	Glu	Gly	Arg	Ile	Thr	Asp	Val	Ile	Pro	Ser	Glu	Ala	Ile	Asn	
			195					200					205				
65	gag	ctc	act	gtt	ctg	gtg	ctg	gtt	aac	acc	att	tac	ttc	aag	ggc	ctg	672
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5	aag gct gat gga gag tcg tgt tca gca tct atg atg tac cag gaa ggc	768
	Lys Ala Asp Gly Glu Ser Cys Ser Ala Ser Met Met Tyr Gln Glu Gly	
	245 250 255	
10	aag ttc cgt tat cgg cgc gtg gct gaa ggc acc cag gtg ctt gag ttg	816
	Lys Phe Arg Tyr Arg Arg Val Ala Glu Gly Thr Gln Val Leu Glu Leu	
	260 265 270	
15	ccc ttc aaa ggt gat gac atc acc atg gtc ctc atc ttg ccc aag cct	864
	Pro Phe Lys Gly Asp Asp Ile Thr Met Val Leu Ile Leu Pro Lys Pro	
	275 280 285	
20	gag aag agc ctg gcc aag gtg gag aag gaa ctc acc cca gag gtg ctg	912
	Glu Lys Ser Leu Ala Lys Val Glu Lys Glu Leu Thr Pro Glu Val Leu	
	290 295 300	
25	cag gag tgg ctg gat gaa ttg gag gag atg atg ctg gtg gtc cac atg	960
	Gln Glu Trp Leu Asp Glu Leu Glu Glu Met Met Leu Val Val His Met	
	305 310 315 320	
30	ccc cgc ttc cgc att gag gac ggc ttc agt ttg aag gag cag ctg caa	1008
	Pro Arg Phe Arg Ile Glu Asp Gly Phe Ser Leu Lys Glu Gln Leu Gln	
	325 330 335	
35	gac atg ggc ctt gtc gat ctg ttc agc cct gaa aag tcc aaa ctc cca	1056
	Asp Met Gly Leu Val Asp Leu Phe Ser Pro Glu Lys Ser Lys Leu Pro	
	340 345 350	
40	ggt att gtt gca gaa ggc cga gat gac ctc tat gtc tca gat gca ttc	1104
	Gly Ile Val Ala Glu Gly Arg Asp Asp Leu Tyr Val Ser Asp Ala Phe	
	355 360 365	
45	cat aag gca ttt ctt gag gta aat gaa gaa ggc agt gaa gca gct gca	1152
	His Lys Ala Phe Leu Glu Val Asn Glu Glu Gly Ser Glu Ala Ala Ala	
	370 375 380	
50	agt acc gct gtt gtg att gct ggc cgt cag cta aac ccc aac agg gtg	1200
	Ser Thr Ala Val Val Ile Ala Gly Arg Gln Leu Asn Pro Asn Arg Val	
	385 390 395 400	
55	act ttc aag gcc aac agg cct ttc ctg gtt ttt ata aga gaa gtt cct	1248
	Thr Phe Lys Ala Asn Arg Pro Phe Leu Val Phe Ile Arg Glu Val Pro	
	405 410 415	
60	ctg aac act att atc ttc atg ggc aga gta gcc aac cct tgt gtt aag	1296
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10	Asp	Glu	Gly	Ser	Glu	Gln	Lys	Ile	Pro	Glu	Ala	Thr	Asn	Arg	Arg	Val	
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15	Trp	Glu	Leu	Ser	Lys	Ala	Asn	Ser	Arg	Phe	Ala	Thr	Thr	Phe	Tyr	Gln	
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	65					70					75					80	
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					85					90					95		
30	Asp	Thr	Leu	Gln	Gln	Leu	Met	Glu	Val	Phe	Lys	Phe	Asp	Thr	Ile	Ser	
				100					105					110			
35	Glu	Lys	Thr	Ser	Asp	Gln	Ile	His	Phe	Phe	Phe	Ala	Lys	Leu	Asn	Cys	
			115					120					125				
40	Arg	Leu	Tyr	Arg	Lys	Ala	Gln	Lys	Ser	Ser	Lys	Leu	Val	Ser	Ala	Asn	
		130					135					140					
45	Arg	Leu	Phe	Gly	Asp	Lys	Ser	Leu	Thr	Phe	Asn	Glu	Thr	Tyr	Gln	Asp	
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50	Ile	Ser	Glu	Leu	Val	Tyr	Gly	Ala	Lys	Leu	Gln	Pro	Leu	Asp	Phe	Lys	
					165					170					175		
55	Glu	Asn	Ala	Glu	Gln	Ser	Arg	Ala	Ala	Ile	Asn	Lys	Trp	Val	Ser	Asn	
				180					185					190			
60	Lys	Thr	Glu	Gly	Arg	Ile	Thr	Asp	Val	Ile	Pro	Ser	Glu	Ala	Ile	Asn	
			195					200					205				
65	Glu	Leu	Thr	Val	Leu	Val	Leu	Val	Asn	Thr	Ile	Tyr	Phe	Lys	Gly	Leu	
		210					215					220					
70	Trp	Lys	Ser	Lys	Phe	Ser	Pro	Glu	Asn	Thr	Arg	Lys	Glu	Leu	Phe	Tyr	
	225					230					235					240	

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					245					250					255	
5	Lys	Phe	Arg	Tyr	Arg	Arg	Val	Ala	Glu	Gly	Thr	Gln	Val	Leu	Glu	Leu
				260					265					270		
10	Pro	Phe	Lys	Gly	Asp	Asp	Ile	Thr	Met	Val	Leu	Ile	Leu	Pro	Lys	Pro
			275					280					285			
15	Glu	Lys	Ser	Leu	Ala	Lys	Val	Glu	Lys	Glu	Leu	Thr	Pro	Glu	Val	Leu
		290					295					300				
20	Gln	Glu	Trp	Leu	Asp	Glu	Leu	Glu	Glu	Met	Met	Leu	Val	Val	His	Met
	305					310					315					320
25	Pro	Arg	Phe	Arg	Ile	Glu	Asp	Gly	Phe	Ser	Leu	Lys	Glu	Gln	Leu	Gln
					325					330					335	
30	Asp	Met	Gly	Leu	Val	Asp	Leu	Phe	Ser	Pro	Glu	Lys	Ser	Lys	Leu	Pro
				340					345					350		
35	Gly	Ile	Val	Ala	Glu	Gly	Arg	Asp	Asp	Leu	Tyr	Val	Ser	Asp	Ala	Phe
			355					360					365			
40	His	Lys	Ala	Phe	Leu	Glu	Val	Asn	Glu	Glu	Gly	Ser	Glu	Ala	Ala	Ala
		370					375					380				
45	Ser	Thr	Ala	Val	Val	Ile	Ala	Gly	Arg	Gln	Leu	Asn	Pro	Asn	Arg	Val
	385					390					395					400
50	Thr	Phe	Lys	Ala	Asn	Arg	Pro	Phe	Leu	Val	Phe	Ile	Arg	Glu	Val	Pro
					405					410					415	
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<210> 67

<211> 1299

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<222> (1)..(1299)

<400> 67

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	Met	Asn	Pro	Met	Cys	Ile	Tyr	Arg	Ser	Pro	Glu	Lys	Lys	Ala	Thr	Glu	
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10	gat	gag	ggc	tca	gaa	cag	aag	atc	ccg	gag	gcc	acc	aac	cgg	cgt	gtc	144
	Asp	Glu	Gly	Ser	Glu	Gln	Lys	Ile	Pro	Glu	Ala	Thr	Asn	Arg	Arg	Val	
			35					40					45				
15	tgg	gaa	ctg	tcc	aag	gcc	aat	tcc	cgc	ttt	gct	acc	act	ttc	tat	cag	192
	Trp	Glu	Leu	Ser	Lys	Ala	Asn	Ser	Arg	Phe	Ala	Thr	Thr	Phe	Tyr	Gln	
		50					55				60						
20	cac	ctg	gca	gat	tcc	aag	aat	gac	aat	gat	aac	att	ttc	ctg	tca	ccc	240
	His	Leu	Ala	Asp	Ser	Lys	Asn	Asp	Asn	Asp	Asn	Ile	Phe	Leu	Ser	Pro	
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25	ctg	agt	atc	tcc	acg	gct	ttt	gct	atg	acc	aag	ctg	ggg	gcc	tgt	aat	288
	Leu	Ser	Ile	Ser	Thr	Ala	Phe	Ala	Met	Thr	Lys	Leu	Gly	Ala	Cys	Asn	
				85						90					95		
30	gac	acc	ctc	cag	caa	ctg	atg	gag	gta	ttt	aag	ttt	gac	acc	ata	tct	336
	Asp	Thr	Leu	Gln	Gln	Leu	Met	Glu	Val	Phe	Lys	Phe	Asp	Thr	Ile	Ser	
			100						105					110			
35	gag	aaa	aca	tct	gat	cag	atc	cac	ttc	ttc	ttt	gcc	aaa	ctg	aac	tgc	384
	Glu	Lys	Thr	Ser	Asp	Gln	Ile	His	Phe	Phe	Phe	Ala	Lys	Leu	Asn	Cys	
			115					120					125				
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	Arg	Leu	Tyr	Arg	Lys	Ala	Gln	Lys	Ser	Ser	Lys	Leu	Val	Ser	Ala	Asn	
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45	cgc	ctt	ttt	gga	gac	aaa	tcc	ctt	acc	ttc	aat	gag	acc	tac	cag	gac	480
	Arg	Leu	Phe	Gly	Asp	Lys	Ser	Leu	Thr	Phe	Asn	Glu	Thr	Tyr	Gln	Asp	
	145					150					155					160	
50	atc	agt	gag	ttg	gta	tat	gga	gcc	aag	ctc	cag	ccc	ctg	gac	ttc	aag	528
	Ile	Ser	Glu	Leu	Val	Tyr	Gly	Ala	Lys	Leu	Gln	Pro	Leu	Asp	Phe	Lys	
				165						170					175		
55	gaa	aat	gca	gag	caa	tcc	aga	gcg	gcc	atc	aac	aaa	tgg	gtg	tcc	aat	576
	Glu	Asn	Ala	Glu	Gln	Ser	Arg	Ala	Ala	Ile	Asn	Lys	Trp	Val	Ser	Asn	
			180						185					190			
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	Lys	Thr	Glu	Gly	Arg	Ile	Thr	Asp	Val	Ile	Pro	Ser	Glu	Ala	Ile	Asn	
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65	gag	ctc	act	gtt	ctg	gtg	ctg	gtt	aac	acc	att	tac	ttc	aag	ggc	ctg	672
	Glu	Leu	Thr	Val	Leu	Val	Val	Val	Asn	Thr	Ile	Tyr	Phe	Lys	Gly	Leu	
		210					215					220					
70	tgg	aag	tca	aag	ttc	agc	cct	gag	aac	aca	agg	aag	gaa	ctg	ttc	tac	720
	Trp	Lys	Ser	Lys	Phe	Ser	Pro	Glu	Asn	Thr	Arg	Lys	Glu	Leu	Phe	Tyr	
	225					230					235					240	

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	Lys Ala Asp Gly Glu Ser Cys Ser Ala Ser Met Met Tyr Gln Glu Gly	
	245 250 255	
5	aag ttc cgt tat cgg cgc gtg gct gaa ggc acc cag gtg ctt gag ttg	816
	Lys Phe Arg Tyr Arg Arg Val Ala Glu Gly Thr Gln Val Leu Glu Leu	
	260 265 270	
10	ccc ttc aaa ggt gat gac atc acc atg gtc ctc atc ttg ccc aag cct	864
	Pro Phe Lys Gly Asp Asp Ile Thr Met Val Leu Ile Leu Pro Lys Pro	
	275 280 285	
15	gag aag agc ctg gcc aag gtg gag aag gaa ctc acc cca gag gtg ctg	912
	Glu Lys Ser Leu Ala Lys Val Glu Lys Glu Leu Thr Pro Glu Val Leu	
	290 295 300	
20	cag gag tgg ctg gat gaa ttg gag gag atg atg ctg gtg gtc cac atg	960
	Gln Glu Trp Leu Asp Glu Leu Glu Glu Met Met Leu Val Val His Met	
	305 310 315 320	
25	ccc cgc ttc cgc att gag gac ggc ttc agt ttg aag gag cag ctg caa	1008
	Pro Arg Phe Arg Ile Glu Asp Gly Phe Ser Leu Lys Glu Gln Leu Gln	
	325 330 335	
30	gac atg ggc ctt gtc gat ctg ttc agc cct gaa aag tcc aaa ctc cca	1056
	Asp Met Gly Leu Val Asp Leu Phe Ser Pro Glu Lys Ser Lys Leu Pro	
	340 345 350	
35	ggt att gtt gca gaa ggc cga gat gac ctc tat gtc tca gat gca ttc	1104
	Gly Ile Val Ala Glu Gly Arg Asp Asp Leu Tyr Val Ser Asp Ala Phe	
	355 360 365	
40	cat aag gca ttt ctt gag gta aat gaa gaa ggc agt gaa gca gct gca	1152
	His Lys Ala Phe Leu Glu Val Asn Glu Glu Gly Ser Glu Ala Ala Ala	
	370 375 380	
45	agt acc gct gtt gtg att gct ggc cgt gag cta aac ccc aac agg gtg	1200
	Ser Thr Ala Val Val Ile Ala Gly Arg Glu Leu Asn Pro Asn Arg Val	
	385 390 395 400	
50	act ttc aag gcc aac agg cct ttc ctg gtt ttt ata aga gaa gtt cct	1248
	Thr Phe Lys Ala Asn Arg Pro Phe Leu Val Phe Ile Arg Glu Val Pro	
	405 410 415	
55	ctg aac act att atc ttc atg ggc aga gta gcc aac cct tgt gtt aag	1296
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His Gly Ser Pro Val Asp Ile Cys Thr Ala Lys Pro Arg Asp Ile Pro

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5	Met	Asn	Pro	Met	Cys	Ile	Tyr	Arg	Ser	Pro	Glu	Lys	Lys	Ala	Thr	Glu
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15	Trp	Glu	Leu	Ser	Lys	Ala	Asn	Ser	Arg	Phe	Ala	Thr	Thr	Phe	Tyr	Gln
		50					55					60				
20	His	Leu	Ala	Asp	Ser	Lys	Asn	Asp	Asn	Asp	Asn	Ile	Phe	Leu	Ser	Pro
	65					70					75				80	
25	Leu	Ser	Ile	Ser	Thr	Ala	Phe	Ala	Met	Thr	Lys	Leu	Gly	Ala	Cys	Asn
				85						90					95	
30	Asp	Thr	Leu	Gln	Gln	Leu	Met	Glu	Val	Phe	Lys	Phe	Asp	Thr	Ile	Ser
				100					105					110		
35	Glu	Lys	Thr	Ser	Asp	Gln	Ile	His	Phe	Phe	Phe	Ala	Lys	Leu	Asn	Cys
			115					120					125			
40	Arg	Leu	Tyr	Arg	Lys	Ala	Gln	Lys	Ser	Ser	Lys	Leu	Val	Ser	Ala	Asn
		130					135					140				
45	Arg	Leu	Phe	Gly	Asp	Lys	Ser	Leu	Thr	Phe	Asn	Glu	Thr	Tyr	Gln	Asp
	145					150					155					160
50	Ile	Ser	Glu	Leu	Val	Tyr	Gly	Ala	Lys	Leu	Gln	Pro	Leu	Asp	Phe	Lys
				165						170					175	
55	Glu	Asn	Ala	Glu	Gln	Ser	Arg	Ala	Ala	Ile	Asn	Lys	Trp	Val	Ser	Asn
			180						185					190		
60	Lys	Thr	Glu	Gly	Arg	Ile	Thr	Asp	Val	Ile	Pro	Ser	Glu	Ala	Ile	Asn
			195					200					205			
65	Glu	Leu	Thr	Val	Leu	Val	Leu	Val	Asn	Thr	Ile	Tyr	Phe	Lys	Gly	Leu
		210					215					220				
70	Trp	Lys	Ser	Lys	Phe	Ser	Pro	Glu	Asn	Thr	Arg	Lys	Glu	Leu	Phe	Tyr
	225					230					235					240
75	Lys	Ala	Asp	Gly	Glu	Ser	Cys	Ser	Ala	Ser	Met	Met	Tyr	Gln	Glu	Gly

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	245					250					255					
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			275					280					285			
15	Glu	Lys	Ser	Leu	Ala	Lys	Val	Glu	Lys	Glu	Leu	Thr	Pro	Glu	Val	Leu
		290					295					300				
20	Gln	Glu	Trp	Leu	Asp	Glu	Leu	Glu	Glu	Met	Met	Leu	Val	Val	His	Met
	305					310					315					320
25	Pro	Arg	Phe	Arg	Ile	Glu	Asp	Gly	Phe	Ser	Leu	Lys	Glu	Gln	Leu	Gln
					325					330					335	
30	Asp	Met	Gly	Leu	Val	Asp	Leu	Phe	Ser	Pro	Glu	Lys	Ser	Lys	Leu	Pro
				340					345					350		
35	Gly	Ile	Val	Ala	Glu	Gly	Arg	Asp	Asp	Leu	Tyr	Val	Ser	Asp	Ala	Phe
			355					360					365			
40	His	Lys	Ala	Phe	Leu	Glu	Val	Asn	Glu	Glu	Gly	Ser	Glu	Ala	Ala	Ala
		370					375					380				
45	Ser	Thr	Ala	Val	Val	Ile	Ala	Gly	Arg	Glu	Leu	Asn	Pro	Asn	Arg	Val
	385					390					395					400
50	Thr	Phe	Lys	Ala	Asn	Arg	Pro	Phe	Leu	Val	Phe	Ile	Arg	Glu	Val	Pro
					405					410					415	
55	Leu	Asn	Thr	Ile	Ile	Phe	Met	Gly	Arg	Val	Ala	Asn	Pro	Cys	Val	Lys
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<211> 1395

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

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<222> (1)..(1395)

<400> 69

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	1	5						10						15						
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	cac His	ggg Gly	agc Ser 35	cct Pro	gtg Val	gac Asp	atc Ile	tgc Cys 40	aca Thr	gcc Ala	aag Lys	ccg Pro	cgg Arg 45	gac Asp	att Ile	ccc Pro	144			
10	atg Met	aat Asn 50	ccc Pro	atg Met	tgc Cys	att Ile	tac Tyr 55	cgc Arg	tcc Ser	ccg Pro	gag Glu	aag Lys 60	aag Lys	gca Ala	act Thr	gag Glu	192			
15	gat Asp 65	gag Glu	ggc Gly	tca Ser	gaa Glu 70	cag Gln	aag Lys	atc Ile	ccg Pro	gag Glu	gcc Ala 75	acc Thr	aac Asn	cgg Arg	cgt Arg	gtc Val 80	240			
20	tgg Trp	gaa Glu	ctg Leu	tcc Ser 85	aag Lys	gcc Ala	aat Asn	tcc Ser	cgc Arg 90	ttt Phe	gct Ala	acc Thr	act Thr	ttc Phe 95	tat Tyr	cag Gln	288			
	cac His	ctg Leu	gca Ala 100	gat Asp	tcc Ser	aag Lys	aat Asn	gac Asp 105	aat Asn	gat Asp	aac Asn	att Ile	ttc Phe 110	ctg Leu	tca Ser	ccc Pro	336			
25	ctg Leu	agt Ser 115	atc Ile	tcc Ser	acg Thr	gct Ala	ttt Phe 120	gct Ala	atg Met	acc Thr	aag Lys	ctg Leu	ggt Gly 125	gcc Ala	tgt Cys	aat Asn	384			
30	gac Asp 130	acc Thr	ctc Leu	cag Gln	caa Gln	ctg Leu	atg Met 135	gag Glu	gta Val	ttt Phe	aag Lys	ttt Phe 140	gac Asp	acc Thr	ata Ile	tct Ser	432			
35	gag Glu 145	aaa Lys	aca Thr	tct Ser	gat Asp 150	cag Gln	atc Ile	cac His	ttc Phe	ttc Phe	ttt Phe 155	gcc Ala	aaa Lys	ctg Leu	aac Asn	tgc Cys 160	480			
	cga Arg	ctc Leu	tat Tyr	cga Arg 165	aaa Lys	gcc Ala	aac Asn	aaa Lys	tcc Ser 170	tcc Ser	aag Lys	tta Leu	gta Val	tca Ser 175	gcc Ala	aat Asn	528			
40	cgc Arg	ctt Leu	ttt Phe	gga Gly 180	gac Asp	aaa Lys	tcc Ser	ctt Leu	acc Thr 185	ttc Phe	aat Asn	gag Glu	acc Thr 190	tac Tyr	cag Gln	gac Asp	576			
45	atc Ile	agt Ser 195	gag Glu	ttg Leu	gta Val	tat Tyr	gga Gly 200	gcc Ala	aag Lys	ctc Leu	cag Gln	ccc Pro 205	ctg Leu	gac Asp	ttc Phe	aag Lys	624			
50	gaa Glu 210	aat Asn	gca Ala	gag Glu	caa Gln	tcc Ser	aga Arg 215	gcg Ala	gcc Ala	atc Ile	aac Asn	aaa Lys 220	tgg Trp	gtg Val	tcc Ser	aat Asn	672			
	aag Lys 225	acc Thr	gaa Glu	ggc Gly	cga Arg	atc Ile 230	acc Thr	gat Asp	gtc Val	att Ile	ccc Pro 235	tcg Ser	gaa Glu	gcc Ala	atc Ile	aat Asn 240	720			
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				260					265					270					
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	Lys	Ala	Asp	Gly	Glu	Ser	Cys	Ser	Ala	Ser	Met	Met	Tyr	Gln	Glu	Gly			
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	Lys	Phe	Arg	Tyr	Arg	Arg	Val	Ala	Glu	Gly	Thr	Gln	Val	Leu	Glu	Leu			
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	305					310					315					320			
25	gag	aag	agc	ctg	gcc	aag	gtg	gag	aag	gaa	ctc	acc	cca	gag	gtg	ctg		1008	
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	Gln	Glu	Trp	Leu	Asp	Glu	Leu	Glu	Glu	Met	Met	Leu	Val	Val	His	Met			
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40	gac	atg	ggc	ctt	gtc	gat	ctg	ttc	agc	cct	gaa	aag	tcc	aaa	ctc	cca		1152	
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		370					375					380							
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	Gly	Ile	Val	Ala	Glu	Gly	Arg	Asp	Asp	Leu	Tyr	Val	Ser	Asp	Ala	Phe			
					385		390				395					400			
50	cat	aag	gca	ttt	ctt	gag	gta	aat	gaa	gaa	ggc	agt	gaa	gca	gct	gca		1248	
	His	Lys	Ala	Phe	Leu	Glu	Val	Asn	Glu	Glu	Gly	Ser	Glu	Ala	Ala	Ala			
					405					410					415				
55	agt	acc	gct	gtt	gtg	att	gct	ggc	cgt	cag	cta	aac	ccc	aac	agg	gtg		1296	
	Ser	Thr	Ala	Val	Val	Ile	Ala	Gly	Arg	Gln	Leu	Asn	Pro	Asn	Arg	Val			
				420				425						430					
60	act	ttc	aag	gcc	aac	agg	cct	ttc	ctg	gtt	ttt	ata	aga	gaa	gtt	cct		1344	
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<213> Homo sapiens

<400> 70

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10	His	Gly	Ser	Pro	Val	Asp	Ile	Cys	Thr	Ala	Lys	Pro	Arg	Asp	Ile	Pro
			35					40					45			
15	Met	Asn	Pro	Met	Cys	Ile	Tyr	Arg	Ser	Pro	Glu	Lys	Lys	Ala	Thr	Glu
		50					55					60				
20	Asp	Glu	Gly	Ser	Glu	Gln	Lys	Ile	Pro	Glu	Ala	Thr	Asn	Arg	Arg	Val
	65					70					75				80	
25	Trp	Glu	Leu	Ser	Lys	Ala	Asn	Ser	Arg	Phe	Ala	Thr	Thr	Phe	Tyr	Gln
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35	Leu	Ser	Ile	Ser	Thr	Ala	Phe	Ala	Met	Thr	Lys	Leu	Gly	Ala	Cys	Asn
								120					125			
40	Asp	Thr	Leu	Gln	Gln	Leu	Met	Glu	Val	Phe	Lys	Phe	Asp	Thr	Ile	Ser
		130					135					140				
45	Glu	Lys	Thr	Ser	Asp	Gln	Ile	His	Phe	Phe	Phe	Ala	Lys	Leu	Asn	Cys
	145					150					155					160
50	Arg	Leu	Tyr	Arg	Lys	Ala	Asn	Lys	Ser	Ser	Lys	Leu	Val	Ser	Ala	Asn
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55	Arg	Leu	Phe	Gly	Asp	Lys	Ser	Leu	Thr	Phe	Asn	Glu	Thr	Tyr	Gln	Asp
				180					185					190		
60	Ile	Ser	Glu	Leu	Val	Tyr	Gly	Ala	Lys	Leu	Gln	Pro	Leu	Asp	Phe	Lys
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65	Glu	Asn	Ala	Glu	Gln	Ser	Arg	Ala	Ala	Ile	Asn	Lys	Trp	Val	Ser	Asn
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	225					230					235					240	
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					245					250					255		
10	Trp	Lys	Ser	Lys	Phe	Ser	Pro	Glu	Asn	Thr	Arg	Lys	Glu	Leu	Phe	Tyr	
				260					265					270			
15	Lys	Ala	Asp	Gly	Glu	Ser	Cys	Ser	Ala	Ser	Met	Met	Tyr	Gln	Glu	Gly	
			275					280					285				
20	Lys	Phe	Arg	Tyr	Arg	Arg	Val	Ala	Glu	Gly	Thr	Gln	Val	Leu	Glu	Leu	
	290						295					300					
25	Pro	Phe	Lys	Gly	Asp	Asp	Ile	Thr	Met	Val	Leu	Ile	Leu	Pro	Lys	Pro	
	305					310					315					320	
30	Glu	Lys	Ser	Leu	Ala	Lys	Val	Glu	Lys	Glu	Leu	Thr	Pro	Glu	Val	Leu	
					325					330					335		
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	Leu	Ser	Ile	Ser	Thr	Ala	Phe	Ala	Met	Thr	Lys	Leu	Gly	Ala	Cys	Asn	
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 85 90 95

50 cac ctg gca gat tcc aag aat gac aat gat aac att ttc ctg tca ccc 336
 His Leu Ala Asp Ser Lys Asn Asp Asn Asp Asn Ile Phe Leu Ser Pro
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 115 120 125

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 130 135 140

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35 Leu Ser Ile Ser Thr Ala Phe Ala Met Thr Lys Leu Gly Ala Cys Asn
115 120 125

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	Asp	Thr	Leu	Gln	Gln	Leu	Met	Glu	Val	Phe	Lys	Phe	Asp	Thr	Ile	Ser
	130						135						140			
5	Glu	Lys	Thr	Ser	Asp	Gln	Ile	His	Phe	Phe	Phe	Ala	Lys	Leu	Asn	Cys
	145					150					155					160
10	Arg	Leu	Tyr	Arg	Lys	Ala	Gln	Lys	Ser	Ser	Lys	Leu	Val	Ser	Ala	Asn
					165					170					175	
15	Arg	Leu	Phe	Gly	Asp	Lys	Ser	Leu	Thr	Phe	Asn	Glu	Thr	Tyr	Gln	Asp
				180					185					190		
20	Ile	Ser	Glu	Leu	Val	Tyr	Gly	Ala	Lys	Leu	Gln	Pro	Leu	Asp	Phe	Lys
			195					200					205			
25	Glu	Asn	Ala	Glu	Gln	Ser	Arg	Ala	Ala	Ile	Asn	Lys	Trp	Val	Ser	Asn
	210						215					220				
30	Lys	Thr	Glu	Gly	Arg	Ile	Thr	Asp	Val	Ile	Pro	Ser	Glu	Ala	Ile	Asn
	225					230					235					240
35	Glu	Leu	Thr	Val	Leu	Val	Leu	Val	Asn	Thr	Ile	Tyr	Phe	Lys	Gly	Leu
					245					250					255	
40	Trp	Lys	Ser	Lys	Phe	Ser	Pro	Glu	Asn	Thr	Arg	Lys	Glu	Leu	Phe	Tyr
				260					265					270		
45	Lys	Ala	Asp	Gly	Glu	Ser	Cys	Ser	Ala	Ser	Met	Met	Tyr	Gln	Glu	Gly
			275					280					285			
50	Lys	Phe	Arg	Tyr	Arg	Arg	Val	Ala	Glu	Gly	Thr	Gln	Val	Leu	Glu	Leu
	290						295					300				
55	Pro	Phe	Lys	Gly	Asp	Asp	Ile	Thr	Met	Val	Leu	Ile	Leu	Pro	Lys	Pro
	305					310					315					320
60	Glu	Lys	Ser	Leu	Ala	Lys	Val	Glu	Lys	Glu	Leu	Thr	Pro	Glu	Val	Leu
					325					330					335	
65	Gln	Glu	Trp	Leu	Asp	Glu	Leu	Glu	Glu	Met	Met	Leu	Val	Val	His	Met
				340					345					350		
70	Pro	Arg	Phe	Arg	Ile	Glu	Asp	Gly	Phe	Ser	Leu	Lys	Glu	Gln	Leu	Gln
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Asp Met Gly Leu Val Asp Leu Phe Ser Pro Glu Lys Ser Lys Leu Pro
370 375 380

5 Gly Ile Val Ala Glu Gly Arg Asp Asp Leu Tyr Val Ser Asp Ala Phe
385 390 395 400

10 His Lys Ala Phe Leu Glu Val Asn Glu Glu Gly Ser Glu Ala Ala Ala
405 410 415

15 Ser Thr Ala Val Val Ile Ala Gly Arg Gln Leu Asn Pro Asn Arg Val
420 425 430

20 Thr Phe Lys Ala Asn Arg Pro Phe Leu Val Phe Ile Arg Glu Val Pro
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25 Leu Asn Thr Ile Ile Phe Met Gly Arg Val Ala Asn Pro Cys Val Lys
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35 <400> 75

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	Met	Tyr	Ser	Asn	Val	Ile	Gly	Thr	Val	Thr	Ser	Gly	Lys	Arg	Lys	Val	
	1				5					10					15		
5	tat	ctt	ttg	tcc	ttg	ctg	ctc	att	ggc	ttc	tgg	gac	tgc	gtg	acc	tgt	96
	Tyr	Leu	Leu	Ser	Leu	Leu	Leu	Ile	Gly	Phe	Trp	Asp	Cys	Val	Thr	Cys	
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10	cac	ggg	agc	cct	gtg	gac	atc	tgc	aca	gcc	aag	ccg	cgg	gac	att	ccc	144
	His	Gly	Ser	Pro	Val	Asp	Ile	Cys	Thr	Ala	Lys	Pro	Arg	Asp	Ile	Pro	
			35					40					45				
15	atg	aat	ccc	atg	tgc	att	tac	cgc	tcc	ccg	gag	aag	aag	gca	act	gag	192
	Met	Asn	Pro	Met	Cys	Ile	Tyr	Arg	Ser	Pro	Glu	Lys	Lys	Ala	Thr	Glu	
		50					55					60					
20	gat	gag	ggc	tca	gaa	cag	aag	atc	ccg	gag	gcc	acc	aac	cgg	cgt	gtc	240
	Asp	Glu	Gly	Ser	Glu	Gln	Lys	Ile	Pro	Glu	Ala	Thr	Asn	Arg	Arg	Val	
	65					70					75					80	
25	tgg	gaa	ctg	tcc	aag	gcc	aat	tcc	cgc	ttt	gct	acc	act	ttc	tat	cag	288
	Trp	Glu	Leu	Ser	Lys	Ala	Asn	Ser	Arg	Phe	Ala	Thr	Thr	Phe	Tyr	Gln	
					85				90						95		
30																	
35																	
40																	
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55																	

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	cac	ctg	gca	gat	tcc	aag	aat	gac	aat	gat	aac	att	ttc	ctg	tca	ccc	336
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			100					105					110				
5	ctg	agt	atc	tcc	acg	gct	ttt	gct	atg	acc	aag	ctg	ggg	gcc	tgt	aat	384
	Leu	Ser	Ile	Ser	Thr	Ala	Phe	Ala	Met	Thr	Lys	Leu	Gly	Ala	Cys	Asn	
			115					120					125				
10	gac	acc	ctc	cag	caa	ctg	atg	gag	gta	ttt	aag	ttt	gac	acc	ata	tct	432
	Asp	Thr	Leu	Gln	Gln	Leu	Met	Glu	Val	Phe	Lys	Phe	Asp	Thr	Ile	Ser	
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15	gag	aaa	aca	tct	gat	cag	atc	cac	ttc	ttc	ttt	gcc	aaa	ctg	aac	tgc	480
	Glu	Lys	Thr	Ser	Asp	Gln	Ile	His	Phe	Phe	Phe	Ala	Lys	Leu	Asn	Cys	
	145					150					155					160	
20	cga	ctc	tat	cga	aaa	gcc	cag	aaa	tcc	tcc	aag	tta	gta	tca	gcc	aat	528
	Arg	Leu	Tyr	Arg	Lys	Ala	Gln	Lys	Ser	Ser	Lys	Leu	Val	Ser	Ala	Asn	
				165					170						175		
25	cgc	ctt	ttt	gga	gac	aaa	tcc	ctt	acc	ttc	aat	gag	acc	tac	cag	gac	576
	Arg	Leu	Phe	Gly	Asp	Lys	Ser	Leu	Thr	Phe	Asn	Glu	Thr	Tyr	Gln	Asp	
			180					185						190			
30	atc	agt	gag	ttg	gta	tat	gga	gcc	aag	ctc	cag	ccc	ctg	gac	ttc	aag	624
	Ile	Ser	Glu	Leu	Val	Tyr	Gly	Ala	Lys	Leu	Gln	Pro	Leu	Asp	Phe	Lys	
			195					200					205				
35	gaa	aat	gca	gag	caa	tcc	aga	gcg	gcc	atc	aac	aaa	tgg	gtg	tcc	aat	672
	Glu	Asn	Ala	Glu	Gln	Ser	Arg	Ala	Ala	Ile	Asn	Lys	Trp	Val	Ser	Asn	
		210					215					220					
40	aag	acc	gaa	ggc	cga	atc	acc	gat	gtc	att	ccc	tcg	gaa	gcc	atc	aat	720
	Lys	Thr	Glu	Gly	Arg	Ile	Thr	Asp	Val	Ile	Pro	Ser	Glu	Ala	Ile	Asn	
	225					230					235					240	
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	Glu	Leu	Thr	Val	Leu	Val	Leu	Val	Asn	Thr	Ile	Tyr	Phe	Lys	Gly	Leu	
				245					250						255		
50	tgg	aag	tca	aag	ttc	agc	cct	gag	aac	aca	agg	aag	gaa	ctg	ttc	tac	816
	Trp	Lys	Ser	Lys	Phe	Ser	Pro	Glu	Asn	Thr	Arg	Lys	Glu	Leu	Phe	Tyr	
			260					265						270			
55	aag	gct	gat	gga	gag	tcg	tgt	tca	gca	tct	atg	atg	tac	cag	gaa	ggc	864
	Lys	Ala	Asp	Gly	Glu	Ser	Cys	Ser	Ala	Ser	Met	Met	Tyr	Gln	Glu	Gly	
			275					280					285				
60	aag	ttc	cgt	tat	cgg	cgc	gtg	gct	gaa	ggc	acc	cag	gtg	ctt	gag	ttg	912
	Lys	Phe	Arg	Tyr	Arg	Arg	Val	Ala	Glu	Gly	Thr	Gln	Val	Leu	Glu	Leu	
		290					295					300					
65	ccc	ttc	aaa	ggg	gat	gac	atc	acc	atg	gtc	ctc	atc	ttg	ccc	aag	cct	960
	Pro	Phe	Lys	Gly	Asp	Asp	Ile	Thr	Met	Val	Leu	Ile	Leu	Pro	Lys	Pro	
	305					310					315					320	
70	gag	aag	agc	ctg	gcc	aag	gtg	gag	aag	gaa	ctc	acc	cca	gag	gtg	ctg	1008
	Glu	Lys	Ser	Leu	Ala	Lys	Val	Glu	Lys	Glu	Leu	Thr	Pro	Glu	Val	Leu	
				325						330					335		

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	cag gag tgg ctg gat gaa ttg gag gag atg atg ctg gtg gtc cac atg	1056
	Gln Glu Trp Leu Asp Glu Leu Glu Glu Met Met Leu Val Val His Met	
	340 345 350	
5	ccc cgc ttc cgc att gag gac ggc ttc agt ttg aag gag cag ctg caa	1104
	Pro Arg Phe Arg Ile Glu Asp Gly Phe Ser Leu Lys Glu Gln Leu Gln	
	355 360 365	
10	gac atg ggc ctt gtc gat ctg ttc agc cct gaa aag tcc aaa ctc cca	1152
	Asp Met Gly Leu Val Asp Leu Phe Ser Pro Glu Lys Ser Lys Leu Pro	
	370 375 380	
15	ggt att gtt gca gaa ggc cga gat gac ctc tat gtc tca gat gca ttc	1200
	Gly Ile Val Ala Glu Gly Arg Asp Asp Leu Tyr Val Ser Asp Ala Phe	
	385 390 395 400	
20	cat aag gca ttt ctt gag gta aat gaa gaa ggc agt gaa gca gct gca	1248
	His Lys Ala Phe Leu Glu Val Asn Glu Glu Gly Ser Glu Ala Ala Ala	
	405 410 415	
25	agt acc gct gtt gtg att gct ggc cgt gag cta aac ccc aac agg gtg	1296
	Ser Thr Ala Val Val Ile Ala Gly Arg Glu Leu Asn Pro Asn Arg Val	
	420 425 430	
30	act ttc aag gcc aac agg cct ttc ctg gtt ttt ata aga gaa gtt cct	1344
	Thr Phe Lys Ala Asn Arg Pro Phe Leu Val Phe Ile Arg Glu Val Pro	
	435 440 445	
35	ctg aac act att atc ttc atg ggc aga gta gcc aac cct tgt gtt aag	1392
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Met Tyr Ser Asn Val Ile Gly Thr Val Thr Ser Gly Lys Arg Lys Val
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5 Tyr Leu Leu Ser Leu Leu Leu Ile Gly Phe Trp Asp Cys Val Thr Cys
20 25 30

10 His Gly Ser Pro Val Asp Ile Cys Thr Ala Lys Pro Arg Asp Ile Pro
35 40 45

15 Met Asn Pro Met Cys Ile Tyr Arg Ser Pro Glu Lys Lys Ala Thr Glu
50 55 60

20 Asp Glu Gly Ser Glu Gln Lys Ile Pro Glu Ala Thr Asn Arg Arg Val

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	65		70		75		80									
5	Trp	Glu	Leu	Ser	Lys	Ala	Asn	Ser	Arg	Phe	Ala	Thr	Thr	Phe	Tyr	Gln
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10	His	Leu	Ala	Asp	Ser	Lys	Asn	Asp	Asn	Asp	Asn	Ile	Phe	Leu	Ser	Pro
				100					105					110		
15	Leu	Ser	Ile	Ser	Thr	Ala	Phe	Ala	Met	Thr	Lys	Leu	Gly	Ala	Cys	Asn
			115					120					125			
20	Asp	Thr	Leu	Gln	Gln	Leu	Met	Glu	Val	Phe	Lys	Phe	Asp	Thr	Ile	Ser
		130					135					140				
25	Glu	Lys	Thr	Ser	Asp	Gln	Ile	His	Phe	Phe	Phe	Ala	Lys	Leu	Asn	Cys
	145					150					155					160
30	Arg	Leu	Tyr	Arg	Lys	Ala	Gln	Lys	Ser	Ser	Lys	Leu	Val	Ser	Ala	Asn
					165					170					175	
35	Arg	Leu	Phe	Gly	Asp	Lys	Ser	Leu	Thr	Phe	Asn	Glu	Thr	Tyr	Gln	Asp
				180					185					190		
40	Ile	Ser	Glu	Leu	Val	Tyr	Gly	Ala	Lys	Leu	Gln	Pro	Leu	Asp	Phe	Lys
			195					200					205			
45	Glu	Asn	Ala	Glu	Gln	Ser	Arg	Ala	Ala	Ile	Asn	Lys	Trp	Val	Ser	Asn
		210					215					220				
50	Lys	Thr	Glu	Gly	Arg	Ile	Thr	Asp	Val	Ile	Pro	Ser	Glu	Ala	Ile	Asn
	225					230					235					240
55	Glu	Leu	Thr	Val	Leu	Val	Leu	Val	Asn	Thr	Ile	Tyr	Phe	Lys	Gly	Leu
				245					250						255	
60	Trp	Lys	Ser	Lys	Phe	Ser	Pro	Glu	Asn	Thr	Arg	Lys	Glu	Leu	Phe	Tyr
				260					265					270		
65	Lys	Ala	Asp	Gly	Glu	Ser	Cys	Ser	Ala	Ser	Met	Met	Tyr	Gln	Glu	Gly
			275					280					285			
70	Lys	Phe	Arg	Tyr	Arg	Arg	Val	Ala	Glu	Gly	Thr	Gln	Val	Leu	Glu	Leu
		290					295					300				
75	Pro	Phe	Lys	Gly	Asp	Asp	Ile	Thr	Met	Val	Leu	Ile	Leu	Pro	Lys	Pro

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305 310 315 320

5 Glu Lys Ser Leu Ala Lys Val Glu Lys Glu Leu Thr Pro Glu Val Leu
325 330 335

10 Gln Glu Trp Leu Asp Glu Leu Glu Glu Met Met Leu Val Val His Met
340 345 350

15 Pro Arg Phe Arg Ile Glu Asp Gly Phe Ser Leu Lys Glu Gln Leu Gln
355 360 365

20 Asp Met Gly Leu Val Asp Leu Phe Ser Pro Glu Lys Ser Lys Leu Pro
370 375 380

25 Gly Ile Val Ala Glu Gly Arg Asp Asp Leu Tyr Val Ser Asp Ala Phe
385 390 395 400

30 His Lys Ala Phe Leu Glu Val Asn Glu Glu Gly Ser Glu Ala Ala Ala
405 410 415

35 Ser Thr Ala Val Val Ile Ala Gly Arg Glu Leu Asn Pro Asn Arg Val
420 425 430

40 Thr Phe Lys Ala Asn Arg Pro Phe Leu Val Phe Ile Arg Glu Val Pro
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45 Leu Asn Thr Ile Ile Phe Met Gly Arg Val Ala Asn Pro Cys Val Lys
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	1 5 10 15	
5	atg aat ccc atg tgc att tac cgc tcc ccg gag aag aag gca act gag	96
	Met Asn Pro Met Cys Ile Tyr Arg Ser Pro Glu Lys Lys Ala Thr Glu	
	20 25 30	
10	gat gag ggc tca gaa cag aag atc ccg gag gcc acc aac cgg cgt gtc	144
	Asp Glu Gly Ser Glu Gln Lys Ile Pro Glu Ala Thr Asn Arg Arg Val	
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	35					40					45							
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	50					55					60							
10	cac His	ctg Leu	gca Ala	gat Asp	tcc Ser	aag Lys	aat Asn	gac Asp	aat Asn	gat Asp	aac Asn	att Ile	ttc Phe	ctg Leu	tca Ser	ccc Pro	240	
	65					70					75							
15	ctg Leu	agt Ser	atc Ile	tcc Ser	acg Thr	gct Ala	ttt Phe	gct Ala	atg Met	acc Thr	aag Lys	ctg Leu	ggt Gly	gcc Ala	tgt Cys	aat Asn	288	
	85					90					95							
20	gac Asp	acc Thr	ctc Leu	cag Gln	caa Gln	ctg Leu	atg Met	gag Glu	gta Val	ttt Phe	aag Lys	ttt Phe	gac Asp	acc Thr	ata Ile	tct Ser	336	
	100					105					110							
25	gag Glu	aaa Lys	aca Thr	tct Ser	gat Asp	cag Gln	atc Ile	cac His	ttc Phe	ttc Phe	ttt Phe	gcc Ala	aaa Lys	ctg Leu	aac Asn	tgc Cys	384	
	115					120					125							
30	cga Arg	ctc Leu	tat Tyr	cga Arg	aaa Lys	gcc Ala	cag Gln	aaa Lys	tcc Ser	tcc Ser	aag Lys	tta Leu	gta Val	tca Ser	gcc Ala	aat Asn	432	
	130					135					140							
35	cgc Arg	ctt Leu	ttt Phe	gga Gly	gac Asp	aaa Lys	tcc Ser	ctt Leu	acc Thr	ttc Phe	aat Asn	gag Glu	acc Thr	tac Tyr	cag Gln	gac Asp	480	
	145					150					155					160		
40	atc Ile	agt Ser	gag Glu	ttg Leu	gta Val	tat Tyr	gga Gly	gcc Ala	aag Lys	ctc Leu	cag Gln	ccc Pro	ctg Leu	gac Asp	ttc Phe	aag Lys	528	
	165					170					175							
45	gaa Glu	aat Asn	gca Ala	gag Glu	caa Gln	tcc Ser	aga Arg	gcg Ala	gcc Ala	atc Ile	aac Asn	aaa Lys	tgg Trp	gtg Val	tcc Ser	aat Asn	576	
	180					185					190							
50	aag Lys	acc Thr	gaa Glu	ggc Gly	cga Arg	atc Ile	acc Thr	gat Asp	gtc Val	att Ile	ccc Pro	tcg Ser	gaa Glu	gcc Ala	atc Ile	aat Asn	624	
	195					200					205							
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	210					215					220							
60	tgg Trp	aag Lys	tca Ser	aag Lys	ttc Phe	agc Ser	cct Pro	gag Glu	aac Asn	aca Thr	agg Arg	aag Lys	gaa Glu	ctg Leu	ttc Phe	tac Tyr	720	
	225					230					235					240		
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	245					250					255							
70	aag Lys	ttc Phe	cgt Arg	tat Tyr	cgg Arg	cgc Arg	gtg Val	gct Ala	gaa Glu	ggc Gly	acc Thr	cag Gln	gtg Val	ctt Leu	gag Glu	ttg Leu	816	
	260					265					270							
75	ccc Pro	ttc Phe	aaa Lys	ggt Gly	gat Asp	gac Asp	atc Ile	acc Thr	atg Met	gtc Val	ctc Leu	atc Ile	ttg Leu	ccc Pro	aag Lys	cct Pro	864	

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5	gag aag agc ctg gcc aag gtg gag aag gaa ctc acc cca gag gtg ctg Glu Lys Ser Leu Ala Lys Val Glu Lys Glu Leu Thr Pro Glu Val Leu 290 295 300			912
10	cag gag tgg ctg gat gaa ttg gag gag atg atg ctg gtg gtc cac atg Gln Glu Trp Leu Asp Glu Leu Glu Glu Met Met Leu Val Val His Met 305 310 315 320			960
15	ccc cgc ttc cgc att gag gac ggc ttc agt ttg aag gag cag ctg caa Pro Arg Phe Arg Ile Glu Asp Gly Phe Ser Leu Lys Glu Gln Leu Gln 325 330 335			1008
20	gac atg ggc ctt gtc gat ctg ttc agc cct gaa aag tcc aaa ctc cca Asp Met Gly Leu Val Asp Leu Phe Ser Pro Glu Lys Ser Lys Leu Pro 340 345 350			1056
25	ggt att gtt gca gaa ggc cga gat gac ctc tat gtc tca gat gca ttc Gly Ile Val Ala Glu Gly Arg Asp Asp Leu Tyr Val Ser Asp Ala Phe 355 360 365			1104
30	cat aag gca ttt ctt gag gta aat gaa gaa ggc agt gaa gca gct gca His Lys Ala Phe Leu Glu Val Asn Glu Glu Gly Ser Glu Ala Ala Ala 370 375 380			1152
35	agt acc gct gtt gtg att gct ggc cgt tcg cta aac ccc aac agg gtg Ser Thr Ala Val Val Ile Ala Gly Arg Ser Leu Asn Pro Asn Arg Val 385 390 395 400			1200
40	act ttc aag gcc aac agg cct ttc ctg gtt ttt ata aga gaa gtt cct Thr Phe Lys Ala Asn Arg Pro Phe Leu Val Phe Ile Arg Glu Val Pro 405 410 415			1248
45	ctg aac act att atc ttc atg ggc aga gta gcc aac cct tgt gtt aag Leu Asn Thr Ile Ile Phe Met Gly Arg Val Ala Asn Pro Cys Val Lys 420 425 430			1296
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70	Met Asn Pro Met Cys Ile Tyr Arg Ser Pro Glu Lys Lys Ala Thr Glu 20 25 30			
75	Asp Glu Gly Ser Glu Gln Lys Ile Pro Glu Ala Thr Asn Arg Arg Val 35 40 45			

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	Trp	Glu	Leu	Ser	Lys	Ala	Asn	Ser	Arg	Phe	Ala	Thr	Thr	Phe	Tyr	Gln
	50						55					60				
5	His	Leu	Ala	Asp	Ser	Lys	Asn	Asp	Asn	Asp	Asn	Ile	Phe	Leu	Ser	Pro
	65					70					75					80
10	Leu	Ser	Ile	Ser	Thr	Ala	Phe	Ala	Met	Thr	Lys	Leu	Gly	Ala	Cys	Asn
					85					90					95	
15	Asp	Thr	Leu	Gln	Gln	Leu	Met	Glu	Val	Phe	Lys	Phe	Asp	Thr	Ile	Ser
				100					105					110		
20	Glu	Lys	Thr	Ser	Asp	Gln	Ile	His	Phe	Phe	Phe	Ala	Lys	Leu	Asn	Cys
			115					120					125			
25	Arg	Leu	Tyr	Arg	Lys	Ala	Gln	Lys	Ser	Ser	Lys	Leu	Val	Ser	Ala	Asn
	130						135					140				
30	Arg	Leu	Phe	Gly	Asp	Lys	Ser	Leu	Thr	Phe	Asn	Glu	Thr	Tyr	Gln	Asp
	145					150					155					160
35	Ile	Ser	Glu	Leu	Val	Tyr	Gly	Ala	Lys	Leu	Gln	Pro	Leu	Asp	Phe	Lys
					165					170					175	
40	Glu	Asn	Ala	Glu	Gln	Ser	Arg	Ala	Ala	Ile	Asn	Lys	Trp	Val	Ser	Asn
				180					185					190		
45	Lys	Thr	Glu	Gly	Arg	Ile	Thr	Asp	Val	Ile	Pro	Ser	Glu	Ala	Ile	Asn
			195					200					205			
50	Glu	Leu	Thr	Val	Leu	Val	Leu	Val	Asn	Thr	Ile	Tyr	Phe	Lys	Gly	Leu
	210						215					220				
55	Trp	Lys	Ser	Lys	Phe	Ser	Pro	Glu	Asn	Thr	Arg	Lys	Glu	Leu	Phe	Tyr
	225					230					235					240
60	Lys	Ala	Asp	Gly	Glu	Ser	Cys	Ser	Ala	Ser	Met	Met	Tyr	Gln	Glu	Gly
					245					250					255	
65	Lys	Phe	Arg	Tyr	Arg	Arg	Val	Ala	Glu	Gly	Thr	Gln	Val	Leu	Glu	Leu
				260					265					270		
70	Pro	Phe	Lys	Gly	Asp	Asp	Ile	Thr	Met	Val	Leu	Ile	Leu	Pro	Lys	Pro
			275					280					285			

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Glu Lys Ser Leu Ala Lys Val Glu Lys Glu Leu Thr Pro Glu Val Leu
290 295 300

5 Gln Glu Trp Leu Asp Glu Leu Glu Glu Met Met Leu Val Val His Met
305 310 315 320

10 Pro Arg Phe Arg Ile Glu Asp Gly Phe Ser Leu Lys Glu Gln Leu Gln
325 330 335

15 Asp Met Gly Leu Val Asp Leu Phe Ser Pro Glu Lys Ser Lys Leu Pro
340 345 350

20 Gly Ile Val Ala Glu Gly Arg Asp Asp Leu Tyr Val Ser Asp Ala Phe
355 360 365

25 His Lys Ala Phe Leu Glu Val Asn Glu Glu Gly Ser Glu Ala Ala Ala
370 375 380

30 Ser Thr Ala Val Val Ile Ala Gly Arg Ser Leu Asn Pro Asn Arg Val
385 390 395 400

Thr Phe Lys Ala Asn Arg Pro Phe Leu Val Phe Ile Arg Glu Val Pro
405 410 415

35 Leu Asn Thr Ile Ile Phe Met Gly Arg Val Ala Asn Pro Cys Val Lys
420 425 430

40 <210> 79
<211> 1395
<212> DNA
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45 <220>
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<222> (1)..(1395)

50 <400> 79

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	Met	Tyr	Ser	Asn	Val	Ile	Gly	Thr	Val	Thr	Ser	Gly	Lys	Arg	Lys	Val	
	1				5					10					15		
5	tat	ctt	ttg	tcc	ttg	ctg	ctc	att	ggc	ttc	tgg	gac	tgc	gtg	acc	tgt	96
	Tyr	Leu	Leu	Ser	Leu	Leu	Leu	Ile	Gly	Phe	Trp	Asp	Cys	Val	Thr	Cys	
				20					25					30			
10	cac	ggg	agc	cct	gtg	gac	atc	tgc	aca	gcc	aag	ccg	cgg	gac	att	ccc	144
	His	Gly	Ser	Pro	Val	Asp	Ile	Cys	Thr	Ala	Lys	Pro	Arg	Asp	Ile	Pro	
			35					40					45				
	atg	aat	ccc	atg	tgc	att	tac	cgc	tcc	ccg	gag	aag	aag	gca	act	gag	192
15																	
20																	
25																	
30																	
35																	
40																	
45																	
50																	
55																	

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	Met	Asn	Pro	Met	Cys	Ile	Tyr	Arg	Ser	Pro	Glu	Lys	Lys	Ala	Thr	Glu	
	50						55					60					
5	gat	gag	ggc	tca	gaa	cag	aag	atc	ccg	gag	gcc	acc	aac	cgg	cgt	gtc	240
	Asp	Glu	Gly	Ser	Glu	Gln	Lys	Ile	Pro	Glu	Ala	Thr	Asn	Arg	Arg	Val	
	65					70					75					80	
10	tgg	gaa	ctg	tcc	aag	gcc	aat	tcc	cgc	ttt	gct	acc	act	ttc	tat	cag	288
	Trp	Glu	Leu	Ser	Lys	Ala	Asn	Ser	Arg	Phe	Ala	Thr	Thr	Phe	Tyr	Gln	
					85				90						95		
15	cac	ctg	gca	gat	tcc	aag	aat	gac	aat	gat	aac	att	ttc	ctg	tca	ccc	336
	His	Leu	Ala	Asp	Ser	Lys	Asn	Asp	Asn	Asp	Asn	Ile	Phe	Leu	Ser	Pro	
				100				105						110			
20	ctg	agt	atc	tcc	acg	gct	ttt	gct	atg	acc	aag	ctg	ggt	gcc	tgt	aat	384
	Leu	Ser	Ile	Ser	Thr	Ala	Phe	Ala	Met	Thr	Lys	Leu	Gly	Ala	Cys	Asn	
			115					120					125				
25	gac	acc	ctc	cag	caa	ctg	atg	gag	gta	ttt	aag	ttt	gac	acc	ata	tct	432
	Asp	Thr	Leu	Gln	Gln	Leu	Met	Glu	Val	Phe	Lys	Phe	Asp	Thr	Ile	Ser	
		130					135					140					
30	gag	aaa	aca	tct	gat	cag	atc	cac	ttc	ttc	ttt	gcc	aaa	ctg	aac	tgc	480
	Glu	Lys	Thr	Ser	Asp	Gln	Ile	His	Phe	Phe	Phe	Ala	Lys	Leu	Asn	Cys	
	145					150					155					160	
35	cga	ctc	tat	cga	aaa	gcc	cag	aaa	tcc	tcc	aag	tta	gta	tca	gcc	aat	528
	Arg	Leu	Tyr	Arg	Lys	Ala	Gln	Lys	Ser	Ser	Lys	Leu	Val	Ser	Ala	Asn	
					165				170						175		
40	cgc	ctt	ttt	gga	gac	aaa	tcc	ctt	acc	ttc	aat	gag	acc	tac	cag	gac	576
	Arg	Leu	Phe	Gly	Asp	Lys	Ser	Leu	Thr	Phe	Asn	Glu	Thr	Tyr	Gln	Asp	
				180					185					190			
45	atc	agt	gag	ttg	gta	tat	gga	gcc	aag	ctc	cag	ccc	ctg	gac	ttc	aag	624
	Ile	Ser	Glu	Leu	Val	Tyr	Gly	Ala	Lys	Leu	Gln	Pro	Leu	Asp	Phe	Lys	
			195				200					205					
50	gaa	aat	gca	gag	caa	tcc	aga	gcg	gcc	atc	aac	aaa	tgg	gtg	tcc	aat	672
	Glu	Asn	Ala	Glu	Gln	Ser	Arg	Ala	Ala	Ile	Asn	Lys	Trp	Val	Ser	Asn	
		210					215					220					
55	aag	acc	gaa	ggc	cga	atc	acc	gat	gtc	att	ccc	tcg	gaa	gcc	atc	aat	720
	Lys	Thr	Glu	Gly	Arg	Ile	Thr	Asp	Val	Ile	Pro	Ser	Glu	Ala	Ile	Asn	
	225					230					235					240	
60	gag	ctc	act	gtt	ctg	gtg	ctg	gtt	aac	acc	att	tac	ttc	aag	ggc	ctg	768
	Glu	Leu	Thr	Val	Leu	Val	Leu	Val	Asn	Thr	Ile	Tyr	Phe	Lys	Gly	Leu	
					245				250						255		
65	tgg	aag	tca	aag	ttc	agc	cct	gag	aac	aca	agg	aag	gaa	ctg	ttc	tac	816
	Trp	Lys	Ser	Lys	Phe	Ser	Pro	Glu	Asn	Thr	Arg	Lys	Glu	Leu	Phe	Tyr	
				260					265					270			
70	aag	gct	gat	gga	gag	tcg	tgt	tca	gca	tct	atg	atg	tac	cag	gaa	ggc	864
	Lys	Ala	Asp	Gly	Glu	Ser	Cys	Ser	Ala	Ser	Met	Met	Tyr	Gln	Glu	Gly	
			275					280					285				
75	aag	ttc	cgt	tat	cgg	cgc	gtg	gct	gaa	ggc	acc	cag	gtg	ctt	gag	ttg	912

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	Lys	Phe	Arg	Tyr	Arg	Arg	Val	Ala	Glu	Gly	Thr	Gln	Val	Leu	Glu	Leu	
	290						295					300					
5	ccc	ttc	aaa	ggt	gat	gac	atc	acc	atg	gtc	ctc	atc	ttg	ccc	aag	cct	960
	Pro	Phe	Lys	Gly	Asp	Asp	Ile	Thr	Met	Val	Leu	Ile	Leu	Pro	Lys	Pro	
	305					310					315					320	
10	gag	aag	agc	ctg	gcc	aag	gtg	gag	aag	gaa	ctc	acc	cca	gag	gtg	ctg	1008
	Glu	Lys	Ser	Leu	Ala	Lys	Val	Glu	Lys	Glu	Leu	Thr	Pro	Glu	Val	Leu	
					325					330					335		
15	cag	gag	tgg	ctg	gat	gaa	ttg	gag	gag	atg	atg	ctg	gtg	gtc	cac	atg	1056
	Gln	Glu	Trp	Leu	Asp	Glu	Leu	Glu	Glu	Met	Met	Leu	Val	Val	His	Met	
				340					345					350			
20	ccc	cgc	ttc	cgc	att	gag	gac	ggc	ttc	agt	ttg	aag	gag	cag	ctg	caa	1104
	Pro	Arg	Phe	Arg	Ile	Glu	Asp	Gly	Phe	Ser	Leu	Lys	Glu	Gln	Leu	Gln	
			355					360					365				
25	gac	atg	ggc	ctt	gtc	gat	ctg	ttc	agc	cct	gaa	aag	tcc	aaa	ctc	cca	1152
	Asp	Met	Gly	Leu	Val	Asp	Leu	Phe	Ser	Pro	Glu	Lys	Ser	Lys	Leu	Pro	
		370					375					380					
30	ggt	att	gtt	gca	gaa	ggc	cga	gat	gac	ctc	tat	gtc	tca	gat	gca	ttc	1200
	Gly	Ile	Val	Ala	Glu	Gly	Arg	Asp	Asp	Leu	Tyr	Val	Ser	Asp	Ala	Phe	
	385					390					395					400	
35	cat	aag	gca	ttt	ctt	gag	gta	aat	gaa	gaa	ggc	agt	gaa	gca	gct	gca	1248
	His	Lys	Ala	Phe	Leu	Glu	Val	Asn	Glu	Glu	Gly	Ser	Glu	Ala	Ala	Ala	
					405					410					415		
40	agt	acc	gct	gtt	gtg	att	gct	ggc	cgt	tcg	cta	aac	ccc	aac	agg	gtg	1296
	Ser	Thr	Ala	Val	Val	Ile	Ala	Gly	Arg	Ser	Leu	Asn	Pro	Asn	Arg	Val	
				420				425						430			
45	act	ttc	aag	gcc	aac	agg	cct	ttc	ctg	gtt	ttt	ata	aga	gaa	gtt	cct	1344
	Thr	Phe	Lys	Ala	Asn	Arg	Pro	Phe	Leu	Val	Phe	Ile	Arg	Glu	Val	Pro	
			435				440						445				
50	ctg	aac	act	att	atc	ttc	atg	ggc	aga	gta	gcc	aac	cct	tgt	gtt	aag	1392
	Leu	Asn	Thr	Ile	Ile	Phe	Met	Gly	Arg	Val	Ala	Asn	Pro	Cys	Val	Lys	
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	Tyr	Leu	Leu	Ser	Leu	Leu	Leu	Ile	Gly	Phe	Trp	Asp	Cys	Val	Thr	Cys	
				20					25					30			

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	His	Gly	Ser	Pro	Val	Asp	Ile	Cys	Thr	Ala	Lys	Pro	Arg	Asp	Ile	Pro
			35					40					45			
5	Met	Asn	Pro	Met	Cys	Ile	Tyr	Arg	Ser	Pro	Glu	Lys	Lys	Ala	Thr	Glu
		50					55					60				
10	Asp	Glu	Gly	Ser	Glu	Gln	Lys	Ile	Pro	Glu	Ala	Thr	Asn	Arg	Arg	Val
	65					70					75				80	
15	Trp	Glu	Leu	Ser	Lys	Ala	Asn	Ser	Arg	Phe	Ala	Thr	Thr	Phe	Tyr	Gln
					85					90					95	
20	His	Leu	Ala	Asp	Ser	Lys	Asn	Asp	Asn	Asp	Asn	Ile	Phe	Leu	Ser	Pro
				100					105					110		
25	Leu	Ser	Ile	Ser	Thr	Ala	Phe	Ala	Met	Thr	Lys	Leu	Gly	Ala	Cys	Asn
			115					120					125			
30	Asp	Thr	Leu	Gln	Gln	Leu	Met	Glu	Val	Phe	Lys	Phe	Asp	Thr	Ile	Ser
		130					135					140				
35	Glu	Lys	Thr	Ser	Asp	Gln	Ile	His	Phe	Phe	Phe	Ala	Lys	Leu	Asn	Cys
	145					150					155					160
40	Arg	Leu	Tyr	Arg	Lys	Ala	Gln	Lys	Ser	Ser	Lys	Leu	Val	Ser	Ala	Asn
					165					170					175	
45	Arg	Leu	Phe	Gly	Asp	Lys	Ser	Leu	Thr	Phe	Asn	Glu	Thr	Tyr	Gln	Asp
				180					185					190		
50	Ile	Ser	Glu	Leu	Val	Tyr	Gly	Ala	Lys	Leu	Gln	Pro	Leu	Asp	Phe	Lys
			195					200					205			
55	Glu	Asn	Ala	Glu	Gln	Ser	Arg	Ala	Ala	Ile	Asn	Lys	Trp	Val	Ser	Asn
		210					215					220				
60	Lys	Thr	Glu	Gly	Arg	Ile	Thr	Asp	Val	Ile	Pro	Ser	Glu	Ala	Ile	Asn
	225					230					235					240
65	Glu	Leu	Thr	Val	Leu	Val	Leu	Val	Asn	Thr	Ile	Tyr	Phe	Lys	Gly	Leu
				245						250					255	
70	Trp	Lys	Ser	Lys	Phe	Ser	Pro	Glu	Asn	Thr	Arg	Lys	Glu	Leu	Phe	Tyr
				260					265					270		

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Lys Ala Asp Gly Glu Ser Cys Ser Ala Ser Met Met Tyr Gln Glu Gly
275 280 285

5 Lys Phe Arg Tyr Arg Arg Val Ala Glu Gly Thr Gln Val Leu Glu Leu
290 295 300

10 Pro Phe Lys Gly Asp Asp Ile Thr Met Val Leu Ile Leu Pro Lys Pro
305 310 315 320

15 Glu Lys Ser Leu Ala Lys Val Glu Lys Glu Leu Thr Pro Glu Val Leu
325 330 335

20 Gln Glu Trp Leu Asp Glu Leu Glu Glu Met Met Leu Val Val His Met
340 345 350

25 Pro Arg Phe Arg Ile Glu Asp Gly Phe Ser Leu Lys Glu Gln Leu Gln
355 360 365

30 Asp Met Gly Leu Val Asp Leu Phe Ser Pro Glu Lys Ser Lys Leu Pro
370 375 380

35 Gly Ile Val Ala Glu Gly Arg Asp Asp Leu Tyr Val Ser Asp Ala Phe
385 390 395 400

His Lys Ala Phe Leu Glu Val Asn Glu Glu Gly Ser Glu Ala Ala Ala
405 410 415

40 Ser Thr Ala Val Val Ile Ala Gly Arg Ser Leu Asn Pro Asn Arg Val
420 425 430

45 Thr Phe Lys Ala Asn Arg Pro Phe Leu Val Phe Ile Arg Glu Val Pro
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<211> 33

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<213> Artificial Sequence

<220>

<223> mutated oligonucleotide

<400> 82

cctgttgggg ttagctgac ggccagcaat cac 33

<210> 83

<211> 33

<212> DNA

<213> Artificial sequence

<220>

<223> mutated oligonucleotide

<400> 83

gtgattgctg gccgtgagct aaacccaac agg 33

<210> 84

<211> 33

<212> DNA

<213> Artificial sequence

<220>

<223> mutated oligonucleotide

<400> 84

cctgttgggg ttagctcac ggccagcaat cac 33

Claims

1. Use of a composition comprising at least a mutated antithrombin having an anticoagulant activity substantially reduced with respect to the anticoagulant activity of the non mutated antithrombin, or having substantially no anti-coagulant activity,
said mutated antithrombin having further:

- a thrombin inhibitory activity substantially reduced, or substantially lost, or
- a factor Xa inhibitory activity reduced, or substantially lost, or
- a thrombin inhibitory activity and a factor Xa inhibitory activity substantially reduced, or substantially lost,

and said mutated antithrombin comprising at least one mutation chosen among the group constituted by:

- R393H, Pro394, Δ R393-S394, Δ R393, Δ S394, S394Q, S394E, N135Q-R393H, N135Q-S394Q, N135Q-S394E, N135Q-Pro394, N135Q- Δ R393-S394, N135Q- Δ R393 and N135Q- Δ S394, the amino acid numbering referring to the antithrombin amino acid sequence represented by SEQ ID NO : 2,
- R425H, Pro426, Δ R425-S426, Δ R425, Δ S426, S426Q, S426E, N167Q-R425H, N167Q-S426Q, N167Q-S426E, N167Q-Pro426, N167Q- Δ R425-S426, N167Q- Δ R425 and N167Q- Δ S426, the amino acid numbering referring to the antithrombin amino acid sequence represented by SEQ ID NO : 26,

for the manufacture of a medicament for the prevention or the treatment of infection, inflammation or hypoxic injury, in particular sepsis and ischemia/reperfusion related to stroke, ischemia/reperfusion related to surgery and ischemia/reperfusion related to organ transplantation.

2. Use according to claim 1, wherein said mutated antithrombin is an amino acid sequence selected:

- from the group consisting of: SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 62, and SEQ ID NO: 64, or
- from the group consisting of: SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:66, and SEQ ID NO:68.

3. Use according to claim 1, wherein

- said mutated antithrombin is an amino acid sequence selected from the group consisting of: SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:70, and SEQ ID NO:72, or
- said mutated antithrombin is an amino acid sequence selected from the group consisting of: SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:42, SEQ ID NO:44, SEQ ID NO:46, SEQ ID NO:48, SEQ ID NO:74 and SEQ ID NO:76.

4. Use of a combination comprising:

- a first antithrombin consisting of at least one mutated antithrombin having a substantially reduced anticoagulant activity, or no anticoagulant activity according to any one of claims 1 to 3, and
- a second antithrombin consisting of at least an antithrombin, having an anticoagulant activity similar to that of the wild type antithrombin

as a combination product for the manufacture of a medicament for the prevention or the treatment of infection, inflammation or hypoxic injury, said combination product suitable for a simultaneous, sequential or separate administration,

said first and said second antithrombins being in a predetermined weight ratio, preferably in a respective weight ratio of about 9:1 to about 1:4.

5. Use of a combination comprising:

- a first antithrombin consisting of at least one mutated antithrombin having a substantially reduced anticoagulant activity, or no anticoagulant activity according to any one of claims 1 to 3, and
- a second antithrombin consisting of at least an antithrombin, having an anticoagulant activity similar to that of the wild type antithrombin

as a combination product for the manufacture of a medicament for the prevention or the treatment of sepsis, said combination product suitable for a simultaneous, sequential or separate administration, said first and said second antithrombins being in a predetermined weight ratio, preferably in a respective weight ratio of about 9:1 to about 1:4.

6. Use of a combination according to claim 4 or 5, wherein

- said first antithrombin is an amino acid sequence selected from the group consisting of SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:18, SEQ ID NO:62, SEQ ID NO:64, and said second antithrombin consisting of the amino acid sequence SEQ ID NO:2, or
- said first antithrombin is an amino acid sequence selected from the group consisting of: SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:42, SEQ ID NO:70 and SEQ ID NO:72, and said second antithrombin consisting of the amino acid sequence SEQ ID NO:26.

7. Use of a combination according to claim 4 or 5, wherein

- said first antithrombin is an amino acid sequence selected from the group consisting of: SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:66 and SEQ ID NO:68, or
- said first antithrombin is an amino acid sequence selected from the group consisting of: SEQ ID NO:38, SEQ

ID NO:40, SEQ ID NO:42, SEQ ID NO:44, SEQ ID NO:46, SEQ ID NO:48, SEQ ID NO:74 and SEQ ID NO:76.

8. Use of a combination according to claim 7, wherein

- said first antithrombin is an amino acid sequence selected from the group consisting of : SEQ ID NO : 14, SEQ ID NO : 16, SEQ ID NO : 20, SEQ ID NO : 22, SEQ ID NO : 24, SEQ ID NO : 66 and SEQ ID NO : 68, said second antithrombin consisting of the amino acid sequence SEQ ID NO:78, or
- said first antithrombin is an amino acid sequence selected from the group consisting of : SEQ ID NO: 38, SEQ ID NO : 40, SEQ ID NO : 44, SEQ ID NO : 46, SEQ ID NO : 48, SEQ ID NO : 74 and SEQ ID NO : 76, said second antithrombin consisting of the amino acid sequence SEQ ID NO:80.

9. Combination comprising at least

- a first antithrombin consisting of at least one mutated antithrombin having a substantially reduced anticoagulant activity, or no anticoagulant activity according to any of claims 1 to 3, and
- a second antithrombin consisting of at least an antithrombin, having an anticoagulant activity similar to that of the wild type antithrombin,

as a combination product for use in a method for the prevention or the treatment of infection, inflammation or hypoxic injury, said combination product being suitable for a simultaneous, sequential or separate administration, said first and said second antithrombins being in a predetermined weight ratio being in a predetermined weight ratio, preferably in a respective weight ratio of about 9:1 to about 1:4.

10. Combination comprising at least

- a first antithrombin consisting of at least one mutated antithrombin having a substantially reduced anticoagulant activity, or no anticoagulant activity according to any of claims 1 to 3, and
- a second antithrombin consisting of at least an antithrombin, having an anticoagulant activity similar to that of the wild type antithrombin,

as a combination product for use in a method for the prevention or the treatment of sepsis, said combination product being suitable for a simultaneous, sequential or separate administration, said first and said second antithrombins being in a predetermined weight ratio being in a predetermined weight ratio, preferably in a respective weight ratio of about 9:1 to about 1:4.

11. Pharmaceutical composition comprising as active ingredient at least a mutated antithrombin, of SEQ ID NO: 62, SEQ ID NO: 64, SEQ ID NO: 66, SEQ ID NO: 68, SEQ ID NO: 70, SEQ ID NO: 72, SEQ ID NO: 74 and SEQ ID NO: 76.

12. Pharmaceutical composition, comprising as active ingredient a combination of the group comprising:

- at least a first antithrombin consisting of one mutated antithrombin having a substantially reduced anticoagulant activity, or substantially no anticoagulant activity according to any one of claims 1 to 3, and
- at least a second antithrombin consisting of at least an antithrombin, having an anticoagulant activity similar to that of the wild type antithrombin,

of the group consisting of the amino acid sequences:

- SEQ ID NO : 4; SEQ ID NO : 6, SEQ ID NO : 8 SEQ ID NO : 10, SEQ ID NO : 18 SEQ ID NO: 62 or SEQ ID NO: 64, in association with SEQ ID NO 2,
- SEQ ID NO : 14, SEQ ID NO : 16,, SEQ ID NO : 20, SEQ ID NO : 22, SEQ ID NO : 24, SEQ ID NO: 66 or SEQ ID NO: 68, in association with SEQ ID NO 2,
- SEQ ID NO : 14, SEQ ID NO : 16,, SEQ ID NO : 20, SEQ ID NO : 22, SEQ ID NO : 24, SEQ ID NO: 66 or SEQ ID NO: 68, in association with SEQ ID NO 78,
- SEQ ID NO : 28, SEQ ID NO : 30, SEQ ID NO : 32, SEQ ID NO : 34, SEQ ID NO : 42; SEQ ID NO: 70 or SEQ ID NO: 72, in association with SEQ ID NO 26,
- SEQ ID NO : 38, SEQ ID NO : 40,, SEQ ID NO : 44, SEQ ID NO : 46, SEQ ID NO : 48, SEQ ID NO: 74 or SEQ ID NO: 76, in association with SEQ ID NO 26, and
- SEQ ID NO : 38, SEQ ID NO : 40, SEQ ID NO : 44, SEQ ID NO : 46, SEQ ID NO : 48, SEQ ID NO: 74 or SEQ

ID NO: 76, in association with SEQ ID NO 80,

in association with a pharmaceutically acceptable vehicle.

- 5 **13.** Mutated antithrombin, which contains at least an amino acid substitution of the amino acid at position 394 of SEQ ID NO:2 by a glutamic acid (Glu) or a Glutamine (Gln), and in particular mutated antithrombin represented by SEQ ID NO: 62 or SEQ ID NO 64,
preferably further comprising a second mutation which is the substitution of the amino acid at position 135, by a Glutamine (Gln), in particular said mutated antithrombin being represented by SEQ ID NO: 66 or 68.
- 10 **14.** Mutated antithrombin, which contains at least an amino acid substitution of the amino acid at position 426 of SEQ ID NO:26 by a glutamic acid (Glu) or a Glutamine (Gln), and in particular mutated antithrombin represented by SEQ ID NO: 70 or SEQ ID NO :72,
preferably further comprising a second mutation which is the substitution of the amino acid at position 167, by a Glutamine (Gln), in particular said mutated antithrombin being represented by SEQ ID NO: 74 or 76.
- 15 **15.** Nucleotide sequence coding for a mutated antithrombin as defined in claim 13 or 14, said nucleic acid sequence being a DNA or an RNA, in particular nucleotide sequences chosen in the group consisting of SEQ ID NO: 61, SEQ ID NO: 63, SEQ ID NO: 65, SEQ ID NO: 67, SEQ ID NO: 69, SEQ ID NO: 71, SEQ ID NO: 73 and SEQ ID NO: 75, or a complementary sequence of said nucleic acid sequence.
- 20

Patentansprüche

- 25 **1.** Verwendung einer Zusammensetzung, umfassend mindestens ein mutiertes Antithrombin mit einer gerinnungshemmenden Aktivität, die in Bezug auf die gerinnungshemmende Aktivität des nicht-mutierten Antithrombins wesentlich verringert ist, oder das im Wesentlichen keine gerinnungshemmende Aktivität aufweist, wobei das mutierte Antithrombin ferner aufweist:
- 30 - eine thrombininhibitorische Aktivität, die wesentlich verringert oder im Wesentlichen verloren ist, oder
- eine Faktor Xa-inhibitorische Aktivität, die wesentlich verringert oder im Wesentlichen verloren ist, oder
- eine thrombininhibitorische Aktivität und eine Faktor Xa-inhibitorische Aktivität, die wesentlich verringert oder im Wesentlichen verloren sind,
- 35 und das mutierte Antithrombin mindestens eine Mutation umfasst, die aus der Gruppe ausgewählt ist, die gebildet wird durch:
- 40 - R393H, Pro394, ΔR393-S394, ΔR393, ΔS394, S394Q, S394E, N135Q-R393H, N135Q-S394Q, N135Q-S394E, N135Q-Pro394, N135Q-ΔR393-S394, N135Q-ΔR393 und N135Q-ΔS394, wobei sich die Aminosäurennummerierung auf die Antithrombin-Aminosäuresequenz bezieht, die durch SEQ ID NO: 2 dargestellt ist,
- R425H, Pro426, ΔR425-S426, ΔR425, ΔS426, S426Q, S426E, N167Q-R425H, N167Q-S426Q, N167Q-S426E, N167Q-Pro426, N167Q-ΔR425-S426, N167Q-ΔR425 und N167Q-ΔS426, wobei sich die Aminosäurennummerierung auf die Antithrombin-Aminosäuresequenz bezieht, die durch SEQ ID NO: 26 dargestellt ist,
- 45 zur Herstellung eines Medikaments zur Vorbeugung oder Behandlung von Infektionen, Entzündungen oder hypoxischen Schädigungen, insbesondere Sepsis und Ischämie / Reperfusion im Zusammenhang mit Schlaganfall, Ischämie / Reperfusion im Zusammenhang mit Chirurgie und Ischämie / Reperfusion im Zusammenhang mit Organtransplantation.
- 50 **2.** Verwendung nach Anspruch 1, wobei das mutierte Antithrombin eine Aminosäuresequenz ist, ausgewählt:
- aus der Gruppe, bestehend aus: SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 62, und SEQ ID NO: 64, oder
- aus der Gruppe, bestehend aus: SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 22, SEQ ID NO: 24, SEQ ID NO: 66, und SEQ ID NO: 68.
- 55 **3.** Verwendung nach Anspruch 1, wobei

- das mutierte Antithrombin eine Aminosäuresequenz ist, die ausgewählt ist aus der Gruppe, bestehend aus: SEQ ID NO: 28, SEQ ID NO: 30, SEQ ID NO: 32, SEQ ID NO: 34, SEQ ID NO: 70, und SEQ ID NO: 72, oder
- das mutierte Antithrombin eine Aminosäuresequenz ist, die ausgewählt ist aus der Gruppe, bestehend aus: SEQ ID NO: 38, SEQ ID NO: 40, SEQ ID NO: 42, SEQ ID NO: 44, SEQ ID NO: 46, SEQ ID NO: 48, SEQ ID NO: 74, und SEQ ID NO: 76.

4. Verwendung einer Kombination, umfassend:

- ein erstes Antithrombin, bestehend aus mindestens einem mutierten Antithrombin mit einer wesentlich verminderten gerinnungshemmenden Aktivität oder keiner gerinnungshemmenden Aktivität nach einem der Ansprüche 1 bis 3, und
- ein zweites Antithrombin, das aus mindestens einem Antithrombin besteht und eine dem Antithrombin des Wildtyps ähnliche gerinnungshemmende Aktivität aufweist

als Kombinationsprodukt zur Herstellung eines Medikaments zur Vorbeugung oder Behandlung von Infektionen, Entzündungen oder hypoxischen Schädigungen, wobei das Kombinationsprodukt für eine gleichzeitige, sequentielle oder getrennte Verabreichung geeignet ist, wobei das erste und das zweite Antithrombin in einem vorbestimmten Gewichtsverhältnis vorliegen, vorzugsweise in einem jeweiligen Gewichtsverhältnis von ungefähr 9:1 bis ungefähr 1:4.

5. Verwendung einer Kombination, umfassend:

- ein erstes Antithrombin, bestehend aus mindestens einem mutierten Antithrombin mit einer wesentlich verminderten gerinnungshemmenden Aktivität oder keiner gerinnungshemmenden Aktivität nach einem der Ansprüche 1 bis 3, und
- ein zweites Antithrombin, das aus mindestens einem Antithrombin besteht und eine dem Antithrombin des Wildtyps ähnliche gerinnungshemmende Aktivität aufweist

als Kombinationsprodukt zur Herstellung eines Medikaments zur Vorbeugung oder Behandlung von Sepsis, wobei das Kombinationsprodukt für eine gleichzeitige, sequentielle oder getrennte Verabreichung geeignet ist, wobei das erste und das zweite Antithrombin in einem vorbestimmten Gewichtsverhältnis vorliegen, vorzugsweise in einem jeweiligen Gewichtsverhältnis von ungefähr 9:1 bis ungefähr 1:4.

6. Verwendung einer Kombination nach Anspruch 4 oder 5, wobei

- das erste Antithrombin eine Aminosäuresequenz ist, die ausgewählt ist aus der Gruppe, bestehend aus SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 18, SEQ ID NO: 62, SEQ ID NO: 64, und das zweite Antithrombin aus der Aminosäuresequenz SEQ ID NO: 2 besteht, oder
- das erste Antithrombin eine Aminosäuresequenz ist, die ausgewählt ist aus der Gruppe, bestehend aus: SEQ ID NO: 28, SEQ ID NO: 30, SEQ ID NO: 32, SEQ ID NO: 34, SEQ ID NO: 42, SEQ ID NO: 70 und SEQ ID NO: 72, und das zweite Antithrombin aus der Aminosäuresequenz SEQ ID NO: 26 besteht.

7. Verwendung einer Kombination nach Anspruch 4 oder 5, wobei

- das erste Antithrombin eine Aminosäuresequenz ist, die ausgewählt ist aus der Gruppe, bestehend aus: SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 20, SEQ ID NO: 22, SEQ ID NO: 24, SEQ ID NO: 66 und SEQ ID NO: 68, oder
- das erste Antithrombin eine Aminosäuresequenz ist, die ausgewählt ist aus der Gruppe, bestehend aus: SEQ ID NO: 38, SEQ ID NO: 40, SEQ ID NO: 42, SEQ ID NO: 44, SEQ ID NO: 46, SEQ ID NO: 48, SEQ ID NO: 74, und SEQ ID NO: 76.

8. Verwendung einer Kombination nach Anspruch 7, wobei

- das erste Antithrombin eine Aminosäuresequenz ist, die ausgewählt ist aus der Gruppe, bestehend aus: SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 20, SEQ ID NO: 22, SEQ ID NO: 24, SEQ ID NO: 66 und SEQ ID NO: 68, und das zweite Antithrombin aus der Aminosäuresequenz SEQ ID NO: 78 besteht, oder
- das erste Antithrombin eine Aminosäuresequenz ist, die ausgewählt ist aus der Gruppe, bestehend aus: SEQ ID NO: 38, SEQ ID NO: 40, SEQ ID NO: 44, SEQ ID NO: 46, SEQ ID NO: 48, SEQ ID NO: 74 und SEQ ID NO:

76, wobei das zweite Antithrombin aus der Aminosäuresequenz SEQ ID NO: 80 besteht.

9. Kombination umfassend mindestens

- ein erstes Antithrombin, bestehend aus mindestens einem mutierten Antithrombin mit einer wesentlich verminderten gerinnungshemmenden Aktivität oder keiner gerinnungshemmenden Aktivität nach einem der Ansprüche 1 bis 3, und
- ein zweites Antithrombin, das aus mindestens einem Antithrombin besteht und eine dem Antithrombin des Wildtyps ähnliche gerinnungshemmende Aktivität aufweist,

als Kombinationsprodukt für die Verwendung in einem Verfahren zur Vorbeugung oder zur Behandlung von Infektionen, Entzündungen oder hypoxischen Schädigungen, wobei das Kombinationsprodukt für eine gleichzeitige, sequentielle oder getrennte Verabreichung geeignet ist, wobei das erste und das zweite Antithrombin in einem vorbestimmten Gewichtsverhältnis vorliegen, in einem vorbestimmten Gewichtsverhältnis vorliegen, vorzugsweise in einem jeweiligen Gewichtsverhältnis von ungefähr 9:1 bis ungefähr 1:4.

10. Kombination umfassend mindestens

- ein erstes Antithrombin, bestehend aus mindestens einem mutierten Antithrombin mit einer wesentlich verminderten gerinnungshemmenden Aktivität oder keiner gerinnungshemmenden Aktivität nach einem der Ansprüche 1 bis 3, und
- ein zweites Antithrombin, das aus mindestens einem Antithrombin besteht und eine dem Antithrombin des Wildtyps ähnliche gerinnungshemmende Aktivität aufweist,

als Kombinationsprodukt für die Verwendung in einem Verfahren zur Vorbeugung oder zur Behandlung von Sepsis, wobei das Kombinationsprodukt für eine gleichzeitige, sequentielle oder getrennte Verabreichung geeignet ist, wobei das erste und das zweite Antithrombin in einem vorbestimmten Gewichtsverhältnis vorliegen, in einem vorbestimmten Gewichtsverhältnis vorliegen, vorzugsweise in einem jeweiligen Gewichtsverhältnis von ungefähr 9:1 bis ungefähr 1:4.

11. Pharmazeutische Zusammensetzung, umfassend als aktiven Bestandteil mindestens ein mutiertes Antithrombin der SEQ ID NO: 62, SEQ ID NO: 64, SEQ ID NO: 66, SEQ ID NO: 68, SEQ ID NO: 70, SEQ ID NO: 72, SEQ ID NO: 74 und SEQ ID NO: 76.

12. Pharmazeutische Zusammensetzung, umfassend als aktiven Bestandteil eine Kombination der Gruppe, umfassend:

- mindestens ein erstes Antithrombin, bestehend aus einem mutierten Antithrombin mit einer wesentlich verringerten gerinnungshemmenden Aktivität oder keiner gerinnungshemmenden Aktivität nach einem der Ansprüche 1 bis 3, und
- mindestens ein zweites Antithrombin, das aus mindestens einem Antithrombin besteht, das eine dem Antithrombin des Wildtyps ähnliche gerinnungshemmende Aktivität aufweist,

aus der Gruppe, bestehend aus den Aminosäuresequenzen:

- SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 18, SEQ ID NO: 62 oder SEQ ID NO: 64, in Verbindung mit SEQ ID NO: 2,
- SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 20, SEQ ID NO: 22, SEQ ID NO: 24, SEQ ID NO: 66 oder SEQ ID NO: 68, in Verbindung mit SEQ ID NO: 2,
- SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 20, SEQ ID NO: 22, SEQ ID NO: 24, SEQ ID NO: 66 oder SEQ ID NO: 68, in Verbindung mit SEQ ID NO: 78,
- SEQ ID NO: 28, SEQ ID NO: 30, SEQ ID NO: 32, SEQ ID NO: 34, SEQ ID NO: 42, SEQ ID NO: 70 oder SEQ ID NO: 72, in Verbindung mit SEQ ID NO: 26,
- SEQ ID NO: 38, SEQ ID NO: 40, SEQ ID NO: 44, SEQ ID NO: 46, SEQ ID NO: 48, SEQ ID NO: 74 oder SEQ ID NO: 76, in Verbindung mit SEQ ID NO: 26, und
- SEQ ID NO: 38, SEQ ID NO: 40, SEQ ID NO: 44, SEQ ID NO: 46, SEQ ID NO: 48, SEQ ID NO: 74 oder SEQ ID NO: 76, in Verbindung mit SEQ ID NO: 80,

in Verbindung mit einem pharmazeutisch verträglichen Träger.

- 5 **13.** Mutiertes Antithrombin, das mindestens eine Aminosäuresubstitution der Aminosäure an Position 394 von SEQ ID NO: 2 durch eine Glutaminsäure (Glu) oder ein Glutamin (Gln) enthält und insbesondere mutiertes Antithrombin, dargestellt durch SEQ ID NO: 62 oder SEQ ID NO: 64, vorzugsweise ferner umfassend eine zweite Mutation, welche die Substitution der Aminosäure an Position 135 ist, durch ein Glutamin (Gln), wobei insbesondere das mutierte Antithrombin durch SEQ ID NO: 66 oder 68 dargestellt wird.
- 10 **14.** Mutiertes Antithrombin, das mindestens eine Aminosäuresubstitution der Aminosäure an Position 426 von SEQ ID NO: 26 durch eine Glutaminsäure (Glu) oder ein Glutamin (Gln) enthält und insbesondere mutiertes Antithrombin, dargestellt durch SEQ ID NO: 70 oder SEQ ID NO: 72, vorzugsweise ferner umfassend eine zweite Mutation, welche die Substitution der Aminosäure an Position 167 ist, durch ein Glutamin (Gln), wobei insbesondere das mutierte Antithrombin durch SEQ ID NO: 74 oder 76 dargestellt wird.
- 15 **15.** Nukleotidsequenz, kodierend für ein mutiertes Antithrombin nach Anspruch 13 oder 14, wobei die Nukleinsäuresequenz eine DNA oder eine RNA ist, insbesondere Nukleotidsequenzen, die ausgewählt sind aus der Gruppe, bestehend aus SEQ ID NO: 61, SEQ ID NO: 63, SEQ ID Nr. 65, SEQ ID Nr. 67, SEQ ID Nr. 69, SEQ ID Nr. 71, SEQ ID Nr. 73 und SEQ ID Nr. 75, oder einer komplementären Sequenz der Nukleinsäuresequenz.
- 20

Revendications

- 25 **1.** Utilisation d'une composition comprenant au moins une antithrombine mutée ayant une activité anticoagulante sensiblement réduite par rapport à l'activité anticoagulante de l'antithrombine non mutée, ou n'ayant sensiblement pas d'activité anticoagulante, ladite antithrombine mutée ayant en outre:
- 30 - une activité inhibitrice de la thrombine sensiblement réduite, ou sensiblement perdue, ou
- une activité inhibitrice du facteur Xa réduite ou sensiblement perdue, ou
- une activité inhibitrice de la thrombine et une activité inhibitrice du facteur Xa sensiblement réduite, ou sensiblement perdue,
- 35 et ladite antithrombine mutée comprenant au moins une mutation choisie dans le groupe constitué par:
- R393H, Pro394, Δ R393-S394, Δ R393, Δ S394, S394Q, S394E, N135Q-R393H, N135Q-S394Q, N135Q-S394E, N135Q-Pro394, N135Q- Δ R393-S394, N135Q- Δ R393 et N135Q- Δ S394, la numérotation des acides aminés se référant à la séquence d'acides aminés de l'antithrombine représenté par SEQ ID NO: 2,
- 40 - R425H, Pro426, Δ R425-S426, Δ R425, Δ S426, S426Q, S426E, N167Q-R425H, N167Q-S426Q, N167Q-S426E, N167Q-Pro426, N167Q- Δ R425-S426, N167Q- Δ R425 et N167Q- Δ S426, la numérotation des acides aminés se référant à la séquence d'acides aminés de l'antithrombine représentée par SEQ ID NO: 26,
- 45 pour la fabrication d'un médicament pour la prévention ou le traitement d'une infection, d'une inflammation ou d'une lésion hypoxique, en particulier une septicémie et une ischémie/ reperfusion liées à un accident vasculaire cérébral, une ischémie/reperfusion liée à une chirurgie et une ischémie/reperfusion liée à une transplantation d'organe.
- 2.** Utilisation selon la revendication 1, dans laquelle ladite antithrombine mutée a une séquence d'acides aminés sélectionnée:
- 50 - dans le groupe consistant en: SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 62, et SEQ ID NO: 64, ou
- dans le groupe consistant en: SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 22, SEQ ID NO: 24, SEQ ID NO: 66, et SEQ ID NO: 68.
- 55 **3.** Utilisation selon la revendication 1, dans laquelle
- ladite antithrombine mutée a une séquence d'acides aminés choisie dans le groupe consistant en: SEQ ID

NO: 28, SEQ ID NO: 30, SEQ ID NO: 32, SEQ ID NO: 34, SEQ ID NO: 70 et SEQ ID NO : 72, ou
 - ladite antithrombine mutée a une séquence d'acides aminés choisie dans le groupe consistant en: SEQ ID
 NO: 38, SEQ ID NO: 40, SEQ ID NO: 42, SEQ ID NO: 44, SEQ ID NO: 46, SEQ ID NO: 48, SEQ ID NO: 74 et
 SEQ ID NO: 76.

4. Utilisation d'une combinaison comprenant:

- une première antithrombine consistant en au moins une antithrombine mutée ayant une activité anticoagulante
 sensiblement réduite, ou pas d'activité anticoagulante selon l'une quelconque des revendications 1 à 3, et
 - une seconde antithrombine consistant en au moins une antithrombine, ayant une activité anticoagulante
 similaire à celle de l'antithrombine sauvage

en tant que produit de combinaison pour la fabrication d'un médicament pour la prévention ou le traitement d'une
 infection, d'une inflammation ou d'une lésion hypoxique, ledit produit de combinaison convenant à une administration
 simultanée, séquentielle ou séparée,
 ladite première et ladite deuxième antithrombine étant dans un rapport de poids prédéterminé, de préférence dans
 un rapport de poids respectif d'environ 9:1 à environ 1:4.

5. Utilisation d'une combinaison comprenant:

- une première antithrombine consistant en au moins une antithrombine mutée ayant une activité anticoagulante
 sensiblement réduite, ou pas d'activité anticoagulante selon l'une quelconque des revendications 1 à 3, et
 - une seconde antithrombine consistant en au moins une antithrombine, ayant une activité anticoagulante
 similaire à celle de l'antithrombine sauvage

en tant que produit de combinaison pour la fabrication d'un médicament pour la prévention ou le traitement d'une
 septicémie, ledit produit de combinaison convenant à une administration simultanée, séquentielle ou séparée,
 ladite première et ladite deuxième antithrombine étant dans un rapport de poids prédéterminé, de préférence dans
 un rapport de poids respectif d'environ 9:1 à environ 1:4.

6. Utilisation d'une combinaison selon la revendication 4 ou 5, dans laquelle

- ladite première antithrombine a une séquence d'acides aminés choisie dans le groupe consistant en SEQ ID
 NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 18, SEQ ID NO: 62, SEQ ID NO: 64, et
 ladite seconde antithrombine consistant en la séquence d'acides aminés SEQ ID NO: 2, ou
 - ladite première antithrombine a une séquence d'acides aminés choisie dans le groupe consistant en: SEQ ID
 NO: 28, SEQ ID NO: 30, SEQ ID NO: 32, SEQ ID NO: 34, SEQ ID NO: 42, SEQ ID NO: 70 et SEQ ID NO: 72,
 et ladite seconde antithrombine consistant en la séquence d'acides aminés SEQ ID NO: 26.

7. Utilisation d'une combinaison selon la revendication 4 ou 5, dans laquelle

- ladite première antithrombine a une séquence d'acides aminés choisie dans le groupe consistant en: SEQ ID
 NO: 14, SEQ ID NO: 16, SEQ ID NO: 20, SEQ ID NO: 22, SEQ ID NO: 24, SEQ ID NO: 66 et SEQ ID NO: 68, ou
 - ladite première antithrombine a une séquence d'acides aminés choisie dans le groupe constitué de: SEQ ID
 NO: 38, SEQ ID NO: 40, SEQ ID NO: 42, SEQ ID NO: 44, SEQ ID NO: 46, SEQ ID NO: 48, SEQ ID NO: 74 et
 SEQ ID NO: 76.

8. Utilisation d'une combinaison selon la revendication 7, dans laquelle

- ladite première antithrombine a une séquence d'acides aminés choisie dans le groupe consistant en: SEQ ID
 NO: 14, SEQ ID NO: 16, SEQ ID NO: 20, SEQ ID NO: 22, SEQ ID NO: 24, SEQ ID NO: 66 et SEQ ID NO: 68,
 ladite seconde antithrombine consistant en la séquence d'acides aminés SEQ ID NO: 78, ou
 - ladite première antithrombine a une séquence d'acides aminés choisie dans le groupe consistant en: SEQ ID
 NO: 38, SEQ ID NO: 40, SEQ ID NO: 44, SEQ ID NO: 46, SEQ ID NO: 48, SEQ ID NO: 74 et SEQ ID NO: 76,
 ladite seconde antithrombine consistant en la séquence d'acides aminés SEQ ID NO: 80.

9. Combinaison comprenant au moins

- une première antithrombine consistant en au moins une antithrombine mutée ayant une activité anticoagulante sensiblement réduite, ou pas d'activité anticoagulante selon l'une quelconque des revendications 1 à 3, et
- une seconde antithrombine consistant en au moins une antithrombine, ayant une activité anticoagulante similaire à celle de l'antithrombine sauvage,

en tant que produit de combinaison destiné à être utilisé dans une méthode pour la prévention ou le traitement d'une infection, d'une inflammation ou d'une lésion hypoxique, ledit produit de combinaison convenant à une administration simultanée, séquentielle ou séparée, ladite première et ladite deuxième antithrombine étant dans un rapport de poids prédéterminé, de préférence dans un rapport de poids respectif d'environ 9:1 à environ 1:4.

10. Combinaison comprenant au moins

- une première antithrombine consistant en au moins une antithrombine mutée ayant une activité anticoagulante sensiblement réduite, ou pas d'activité anticoagulante selon l'une quelconque des revendications 1 à 3, et
- une seconde antithrombine consistant en au moins une antithrombine, ayant une activité anticoagulante similaire à celle de l'antithrombine sauvage,

en tant que produit de combinaison destiné à être utilisé dans une méthode pour la prévention ou le traitement d'une septicémie, ledit produit de combinaison convenant à une administration simultanée, séquentielle ou séparée, ladite première et ladite deuxième antithrombine étant dans un rapport de poids prédéterminé, de préférence dans un rapport de poids respectif d'environ 9:1 à environ 1:4

11. Composition pharmaceutique comprenant comme ingrédient actif au moins une antithrombine mutée, de SEQ ID NO: 62, SEQ ID NO: 64, SEQ ID NO: 66, SEQ ID NO: 68, SEQ ID NO: 70, SEQ ID NO: 72, SEQ ID NO: 74 et SEQ ID NO: 76

12. Composition pharmaceutique, comprenant comme ingrédient actif une combinaison du groupe comprenant:

- au moins une première antithrombine consistant en une antithrombine mutée ayant une activité anticoagulante sensiblement réduite, ou sensiblement aucune activité anticoagulante selon l'une quelconque des revendications 1 à 3, et
- au moins une seconde antithrombine consistant en au moins une antithrombine, ayant une activité anticoagulante similaire à celle de l'antithrombine sauvage,

du groupe consistant en les séquences d'acides aminés:

- SEQ ID NO: 4; SEQ ID NO: 6, SEQ ID NO: 8 SEQ ID NO: 10, SEQ ID NO: 18 SEQ ID NO: 62 ou SEQ ID NO: 64, en association avec SEQ ID NO 2,
- SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 20, SEQ ID NO: 22, SEQ ID NO: 24, SEQ ID NO: 66 ou SEQ ID NO: 68, en association avec SEQ ID NO 2,
- SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 20, SEQ ID NO: 22, SEQ ID NO: 24, SEQ ID NO: 66 ou SEQ ID NO: 68, en association avec SEQ ID NO 78,
- SEQ ID NO: 28, SEQ ID NO: 30, SEQ ID NO: 32, SEQ ID NO: 34, SEQ ID NO: 42; SEQ ID NO: 70 ou SEQ ID NO: 72, en association avec SEQ ID NO 26,
- SEQ ID NO: 38, SEQ ID NO: 40, SEQ ID NO: 44, SEQ ID NO: 46, SEQ ID NO: 48, SEQ ID NO: 74 ou SEQ ID NO: 76, en association avec SEQ ID NO 26, et
- SEQ ID NO: 38, SEQ ID NO: 40, SEQ ID NO: 44, SEQ ID NO: 46, SEQ ID NO: 48, SEQ ID NO: 74 ou SEQ ID NO: 76, en association avec SEQ ID NO 80 ,

en association avec un véhicule pharmaceutiquement acceptable.

13. Antithrombine mutée, qui contient au moins une substitution d'acide aminé de l'acide aminé en position 394 de SEQ ID NO : 2 par un acide glutamique (Glu) ou une glutamine (Gln), et en particulier une antithrombine mutée représentée par SEQ ID NO: 62 ou SEQ ID NO 64, de préférence comprenant de plus une seconde mutation correspondant à la substitution de l'acide aminé en position 135, par une glutamine (Gln), en particulier ladite antithrombine mutée étant représentée par SEQ ID NO: 66 ou 68.

14. Antithrombine mutée, qui contient au moins une substitution d'acide aminé de l'acide aminé en position 426 de SEQ ID NO: 26 par un acide glutamique (Glu) ou une glutamine (Gln), et en particulier une antithrombine mutée représentée par SEQ ID NO: 70 ou SEQ ID NO: 72,
de préférence comprenant de plus une seconde mutation correspondant à la substitution de l'acide aminé en position 167, par une glutamine (Gln), en particulier ladite antithrombine mutée étant représentée par SEQ ID NO: 74 ou 76.
15. Séquence nucléotidique codant pour une antithrombine mutée telle que définie dans la revendication 13 ou 14, ladite séquence d'acides nucléiques étant un ADN ou un ARN, en particulier des séquences nucléotidiques choisies dans le groupe consistant en SEQ ID NO: 61, SEQ ID NO: 63, SEQ ID NO: 65, SEQ ID NO: 67, SEQ ID NO: 69, SEQ ID NO: 71, SEQ ID NO: 73 et SEQ ID NO: 75, ou une séquence complémentaire de ladite séquence d'acides nucléiques.

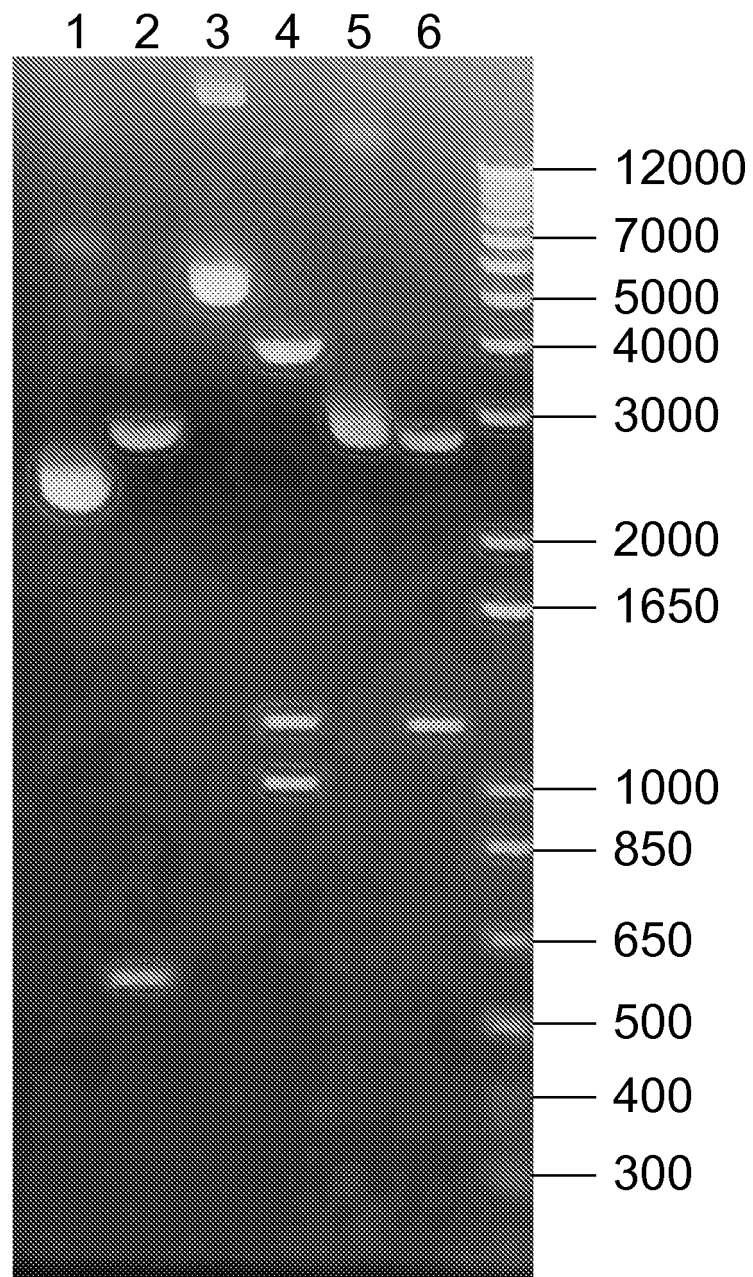


Figure 1

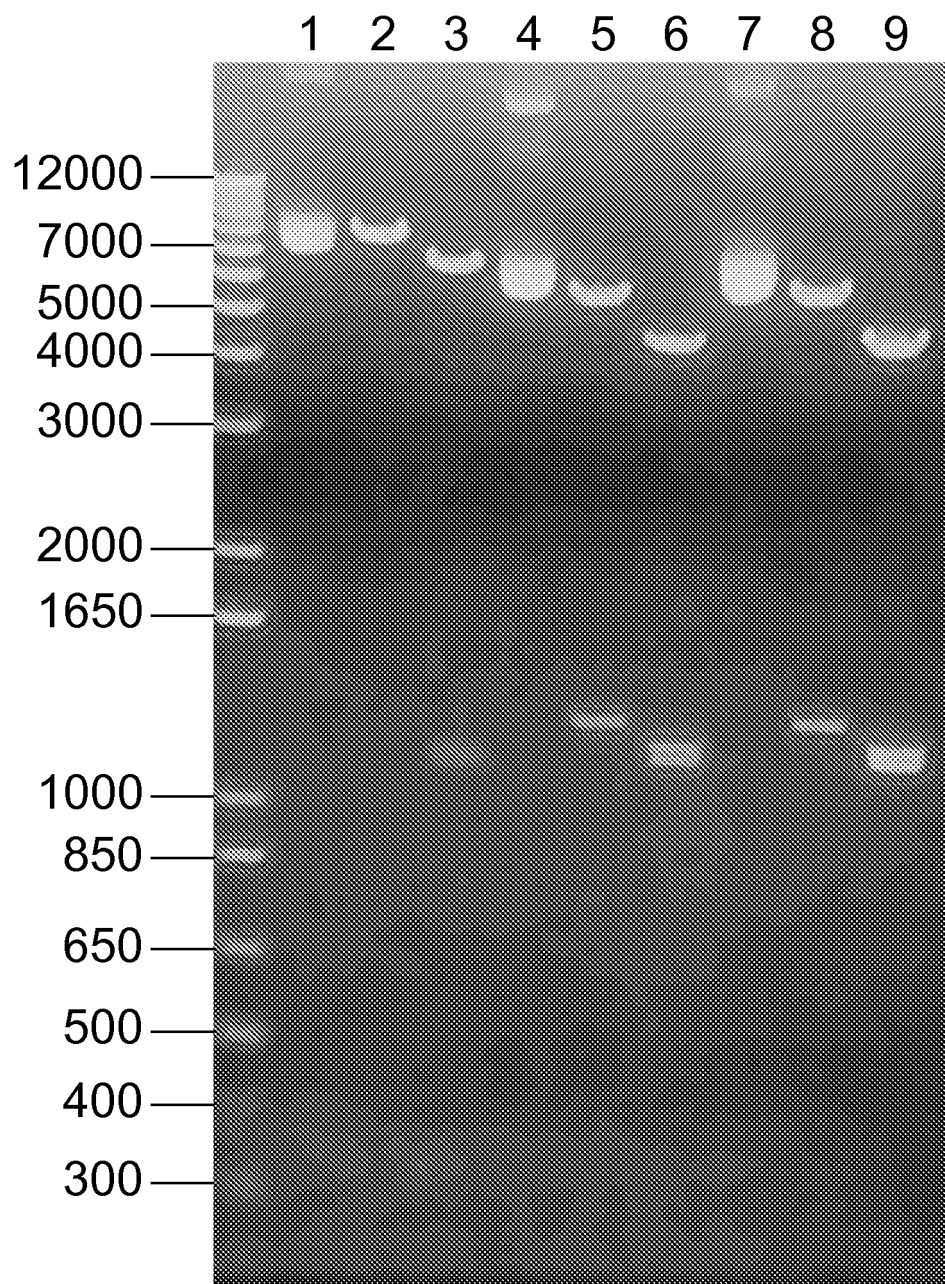


Figure 2

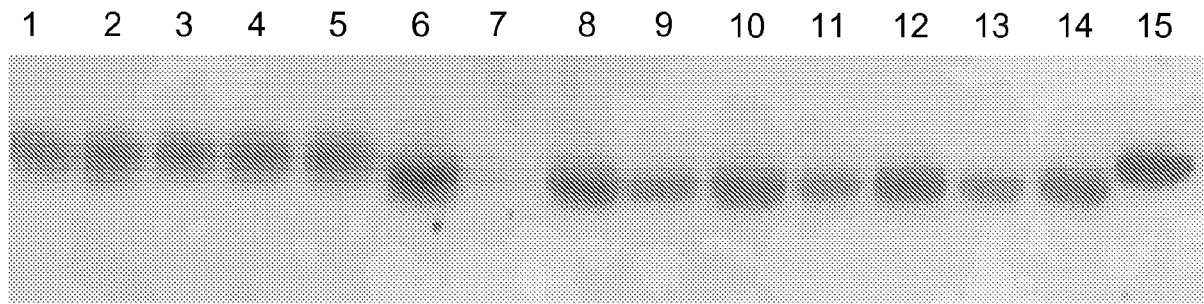


Figure 3

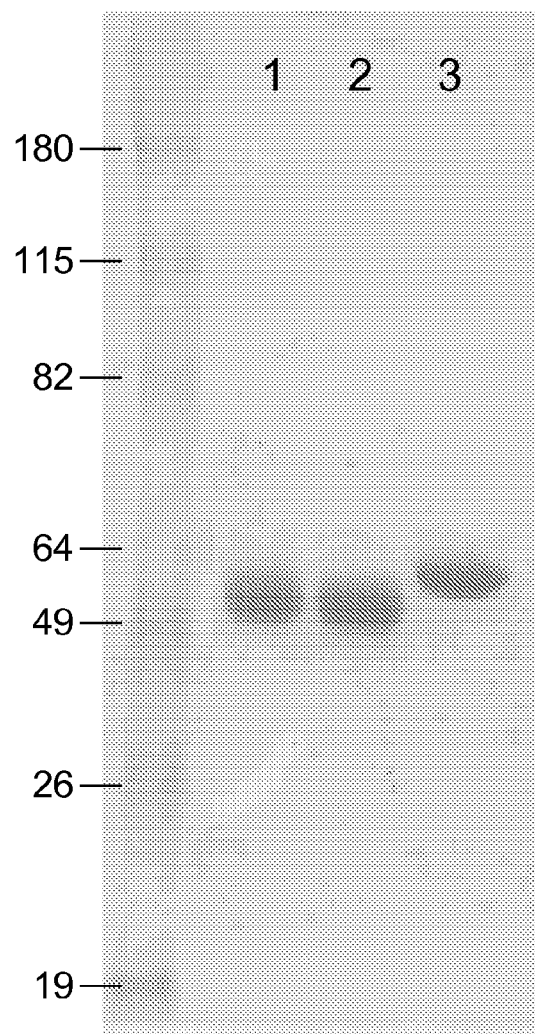


Figure 4

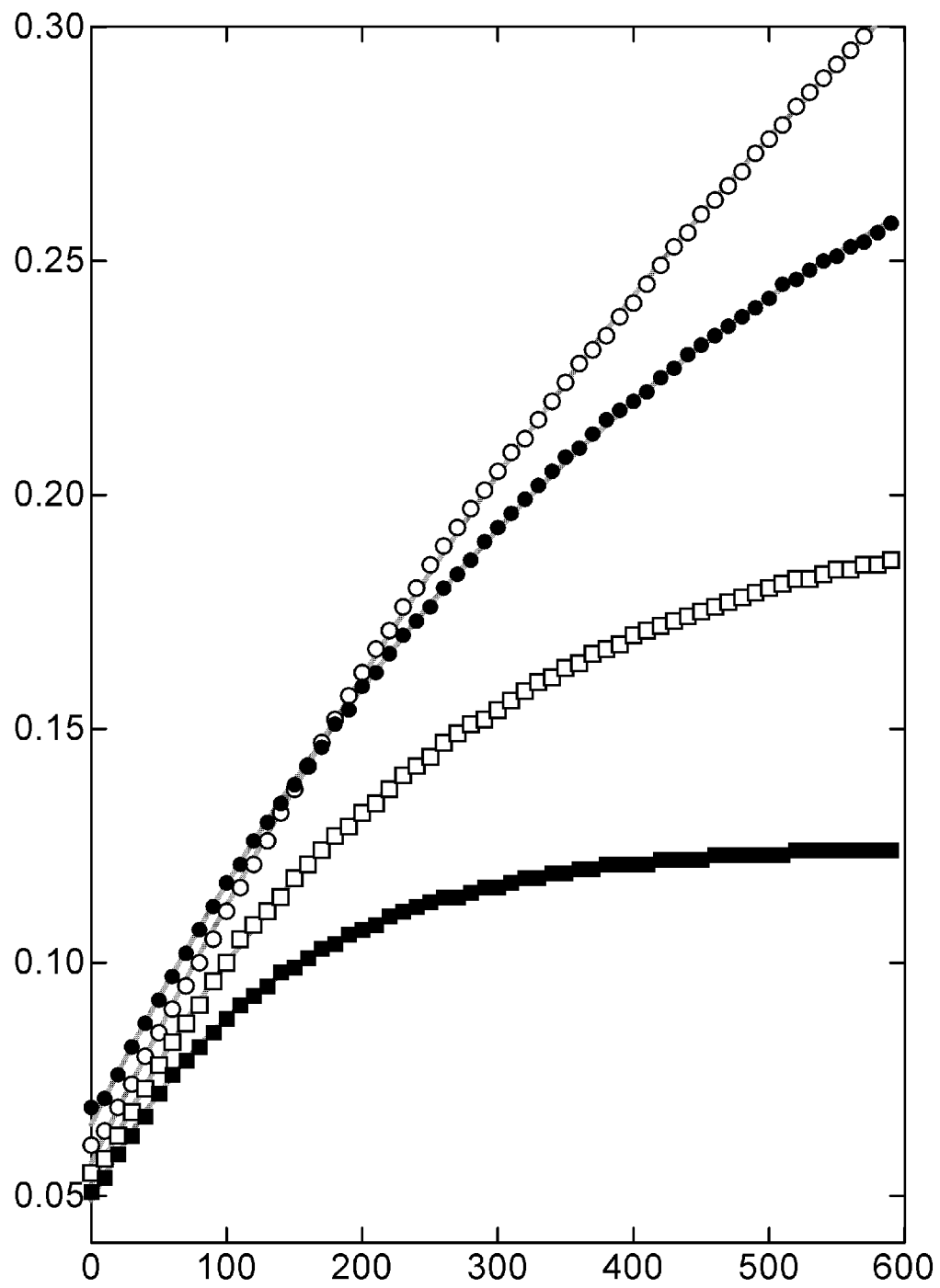


Figure 5A

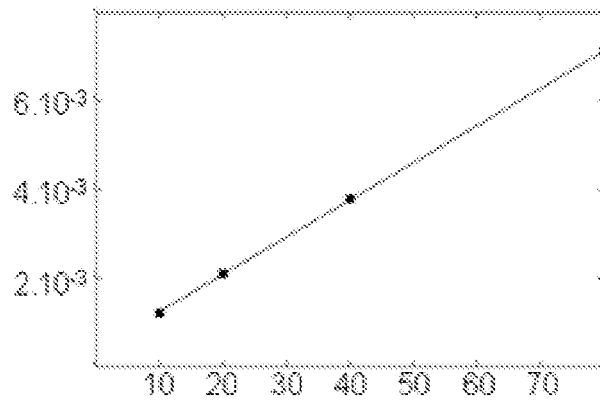


Figure 5B

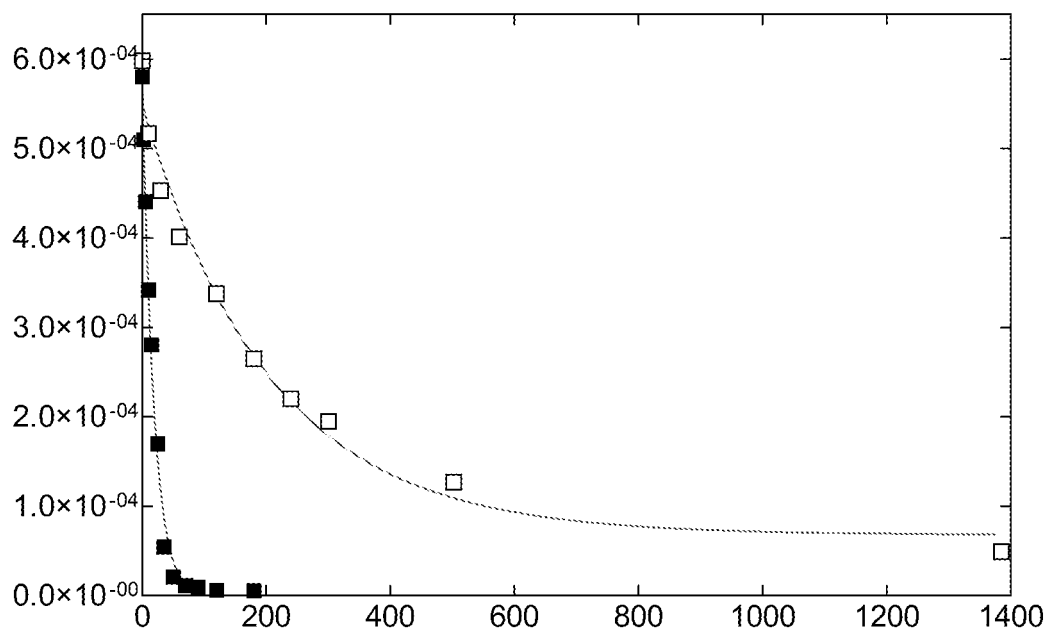


Figure 6

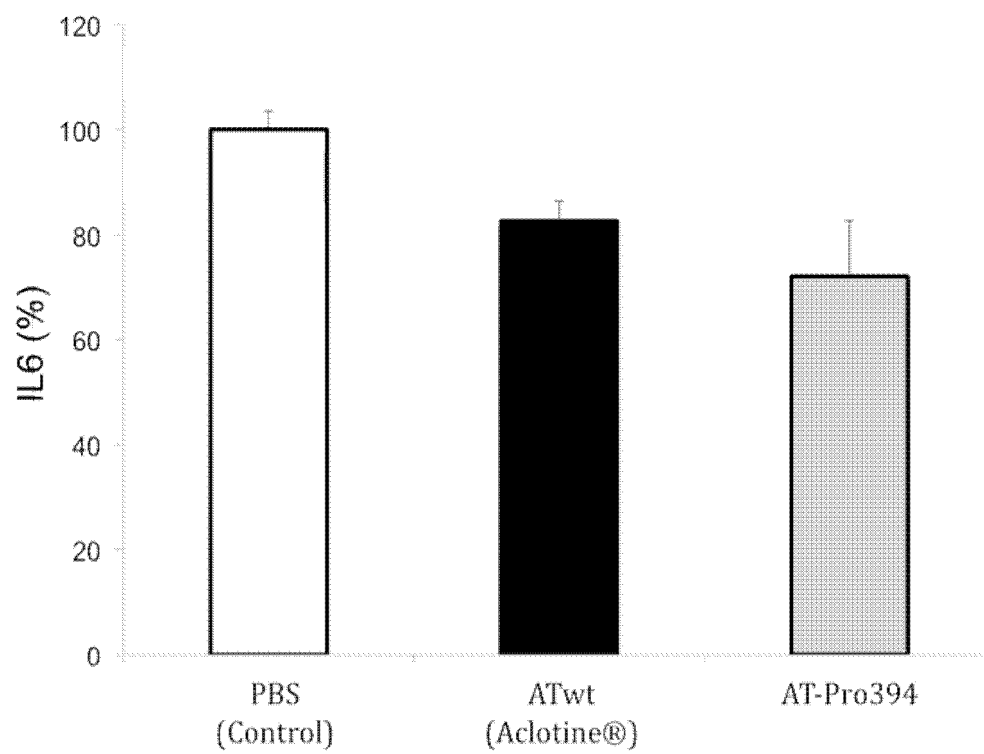


Figure 7

REFERENCES CITED IN THE DESCRIPTION

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